Indicators of fetal growth and adult liver enzymes: The Bogalusa Heart Study and the Cardiovascular Risk in Young Finns Study

Emily W. Harville1 eharvill@tulane.edu

Wei Chen1 wchen1@tulane.edu

Lydia Bazzano1 lbazzano@tulane.edu

Mervi Oikonen2 mervi.oikonen@utu.fi

Nina Hutri-Kähönen3 nina.hutri-kahonen@uta.fi

Olli Raitakari2 olli.raitakari@utu.fi

1 Department of Epidemiology, Tulane School of Public Health and Tropical Medicine, Tulane University, New Orleans, LA

2 Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Finland

3 Department of Pediatrics, University of Tampere and Tampere University Hospital, Tampere, Finland

Corresponding author:

Emily Harville

Associate Professor

Department of Epidemiology

Tulane School of Public Health and Tropical Medicine

Tidewater 2012

1440 Canal St.

New Orleans, LA

USA

eharvill@tulane.edu

Tel. 1-504-988-7327

Fax. 1-504-988-1568

Mailing address:

Epidemiology #8318

1440 CANAL ST STE 2000

NEW ORLEANS LA 70112

Abstract: 244 words

Word count: 2300

6 tables

Running head: Fetal growth and liver enzymes

**Abbreviations**

GGT, gamma-glutamyl transferase

ALT, alanine transaminase

AST, aspartase transaminase

BHS, Bogalusa Heart Study

YF, Cardiovascular Risk in Young Finns Study

OR, Odds ratio

NAFLD, Non-alcoholic fatty liver disease

FLI, Fatty liver index

Despite the interest in the relationship of fetal exposures to adult cardiovascular disease, few studies have examined indicators of adult fatty liver disease as an outcome. Previous results are inconsistent, and indicate possible variation by sex. Adult liver enzymes (gamma-glutamyl transferase (GGT), alanine transaminase (ALT), and aspartase transaminase (AST)) were measured in two cohort studies: the Bogalusa Heart Study (BHS; n=1803) and the Cardiovascular Risk in Young Finns (YF; n=3571) study, which also had ultrasound measures of liver fat (n=2546). Predictors of dichotomized (clinical cut-offs) and continuous (within the reference range) liver enzymes included low birthweight (<2500g), macrosomia (>4000g), small-for-gestational-age (birthweight <10th percentile for gestational age for population), large-for-gestational-age (>90th percentile), and preterm birth. Multiple logistic and linear regression were conducted, adjusted for medical, behavioral, and socioeconomic indicators. Interactions with sex were also examined. In BHS, birth measures were not strongly associated with clinically high levels of liver enzymes, and within the reference range measures of reduced growth were associated with increased AST in women. In the YF study, at least one marker of reduced growth was associated with higher GGT, higher ALT, and higher AST (in women). Probable fatty liver on ultrasound was associated with low birthweight (2.41, 1.42-4.09) and preterm birth (2.84, 1.70-4.76). These results suggest a link between birth parameters and adult fatty liver, but encourage consideration of population variation in these relationships.

# Keywords: birthweight, gestational age, non-alcoholic fatty liver disease, gamma-glutamyltransferase

**Introduction**

In animals, prenatal energy deprivation leads to both growth retardation and adult disease,[1](#_ENREF_1) but so can gestational energy overload.[2](#_ENREF_2) Recently, low birth weight has been associated with non-alcoholic hepatic steatosis (fatty liver disease; FLD) in adulthood in human males.[3](#_ENREF_3) FLD (non-alcoholic) is an indicator of hepatic insulin resistance and the metabolic syndrome. Several liver enzymes indicate fatty liver disease; gamma-glutamyl transferase (GGT) and alanine aminotransferase (ALT), specific markers of liver damage or function, have been most studied.[4](#_ENREF_4) These enzymes have been independently associated with several cardiovascular risk factors and outcomes, even when levels fall within the reference/normal range [5](#_ENREF_5). Other enzymes, such as aspartate transaminase (AST), are also elevated, though not exclusively, in FLD, and have been less studied.[4](#_ENREF_4)

However, human studies of early life influences on liver enzymes are rare. Some studies have been conducted in children, generally finding reduced fetal growth associated increased risk.[6](#_ENREF_6), [7](#_ENREF_7) In adults, one study found a negative association between GGT and birthweight (not statistically significant).[8](#_ENREF_8) In addition, differences by sex have been reported, with at least one study suggesting an inverse association between birthweight and adult GGT/ALT in women, but potentially a direct association in men.[9](#_ENREF_9), [10](#_ENREF_10) Two studies have considered preterm birth: in the ESTER study, Finnish adults who were born preterm had higher risk of fatty liver index (FLI; an index combining information on triglycerides, BMI, GGT, and waist circumference[11](#_ENREF_11)) >30, and to have higher overall ALT and AST levels, but no difference in GGT [12](#_ENREF_12), while a small Dutch study found that accelerated weight gain in infancy was associated with FLI, while birthweight and gestational age were not.[13](#_ENREF_13)

The question of the relationship between birthweight and liver enzymes thus remains an open question, suggesting that further research is needed. Two opposing hypotheses could be put forth on the relationship between birthweight and adult FLD. The first is that those with a genetic or other consistent, lifetime propensity for increased adiposity would be larger at birth and have worse health as adults. The “thrifty phenotype” hypothesis, on the other hand, indicates that prenatal undernutrition, normally indicated by lower birthweight, is associated with adult cardiovascular disease, possibly due to lasting alterations in energy metabolism[14-16](#_ENREF_14). We hypothesized that indicators of reduced fetal growth will be associated with higher levels of liver enzymes and increased indicators of fatty liver in adulthood. In this paper, we examine whether the association between indicators of prenatal growth and health (birthweight and gestational age) predicts adult raised liver enzyme levels, both at a clinical level and within the normal range, and whether this relationship varies by sex. We consider these questions in two long-running studies of child and adult cardiovascular health: the Bogalusa Heart Study and the Cardiovascular Risk in Young Finns.

**Methods**

**Study populations**

The Bogalusa Heart Study (BHS) is a long-running, community-based series of cross-sectional studies conducted in Bogalusa, LA. Data from this analysis were taken from 3 follow-up studies conducted between 1985 and 2002. Standardized protocols were used at each visit, with subjects instructed to fast. For subjects with multiple visits, data at the latest available measurement were used. Among 2598 participants aged 18 and older, 1950 had at least one liver enzyme measurement and one birth outcome measure; there were no differences in sex, race, or BMI between those included and excluded, but the included participants tended to be younger (mean age 31.8 vs. 33.6, p<0.01). After exclusions for pregnant women (n=21), multiple births (n=68), and those lacking fasting blood samples (n=62; some overlap among groups), 1803 observations were left for analysis. Participants were born between 1938 and 1987 (median year=1966).

The Cardiovascular Risk in Young Finns Study (YF) was officially started in 1980 to examine heart disease risk factors in children and adolescents [17](#_ENREF_17" \o "Raitakari, 2008 #414). At baseline, participants were 3-18 years old (i.e., birth years between 1962 and 1977); follow-ups have been regularly conducted every 3-5 years since then, with the most recent in 2011. 3571 participants had data on at least one birth outcome and one liver enzyme. Overall, loss to follow-up has been greater among men, older participants, and smokers.[17](#_ENREF_17) Liver enzymes were measured after 2001; among those who participated in at least one of those exams, whether a participant had liver enzymes measurements did not vary by sex or BMI, but did vary by age (mean age 31.3 vs. 34.7, p<0.01).

**Exposure measurement**. For BHS, data had previously been linked with birth certificates to determine participants’ birthweight and gestational age [18](#_ENREF_18). For YF, participants and their parents reported birthweight and gestational age at an early visit. Such reports, particularly by the mother, have been found to correlate well with clinical records.[19-22](#_ENREF_19) Both absolute and relative measures of birthweight were examined. Low birthweight (LBW) was defined as birthweight <2500g and macrosomia as birthweight >4000 g. Small-for-gestational-age (SGA) was defined as weight <10th percentile and large-for-gestational-age (LGA) as weight >90th percentile for gestation by sex with the study population used to define percentiles. For BHS, the included sample had only 7.9% SGA compared to the original sample used to construct the percentiles, implying that it may be somewhat lower-risk group. Preterm birth (PTB) was defined as birth <37 weeks’ gestation.

**Outcome measurement**. BHS: GGT and ALT levels were measured as part of a multiple chemistry profile (SMA20) by enzymatic procedures with the multichannel Olympus Au-5000 analyzer (Olympus, Lake success, NY). Fatty liver index (FLI) was calculated by the method of Bedogni et al.[11](#_ENREF_11), incorporating GGT, BMI, triglycerides, and waist circumference.

YF: Venous blood samples were drawn after an overnight fast and serum was separated, aliquoted, and stored at -70°C until analysis. From the samples taken in study year 2011, GGT, ALT, and AST concentrations were measured by enzymatic methods (GGT, ALT, AST, Glucose, Cholesterol and Triglycerides System Reagent, Beckman Coulter Biomedical, O’Callaghan’s Mills, Ireland) on an automatic analyzer (AU400, Olympus, Tokyo, Japan) at the laboratory of the Department of Chronic Disease Prevention, National Institute for Health and Welfare, Turku, Finland. From the samples taken in study year 2001, the GGT, ALT and AST concentrations were measured at the Department of Laboratory Medicine, Konventhospital Barmherzige Brueder Linz, Austria, on an ARCHITECT automated analyzer (Abbott Diagnostics, Abbott Parks, IL). In addition, in the Young Finns study, ultrasound imaging of the liver was performed in 2011 for 2,546 study participants using a validated protocol [23](#_ENREF_23) and Sequoia 512 ultrasound mainframes (Acuson, Mountain View, CA, USA) with 4.0 MHz adult abdominal transducers. Evaluation of hepatic steatosis was performed according to liver-to-kidney contrast, parenchymal brightness, deep beam attenuation and bright vessel walls,[24](#_ENREF_24) and the presence of hepatic steatosis was assessed visually by a trained ultrasonographer. The participants were classified into probable fatty liver and normal liver groups.[25](#_ENREF_25) FLI was calculated as for BHS.

**Covariate definitions**. All covariates were measured at the time of the liver enzyme measurement and defined as listed in table 1, unless otherwise specified.

For BHS, physical activity was based on two questions, ranking physical activity at work and outside of work on a 5 point scale. For YF, nonwork physical activity was based on combined information on frequency, intensity, and duration of physical exercise.[26](#_ENREF_26)

**Modeling strategy**. The study designs were thought to differ sufficiently that combining the data for analysis would not be appropriate; therefore, results are presented separately by study.

First, a dichotomous outcome with levels indicating possible clinical concern based on the literature (for men, GGT>68 U/L, ALT>59 U/L; for women, GGT>40 U/L, ALT>41 U/L[27](#_ENREF_27); for all, AST>34 U/L, FLI>=60 [11](#_ENREF_11)) were examined using logistic regression; in addition, ultrasound fatty liver was examined for YF participants. Next, outcomes within the reference range (in order to examine higher-risk individuals without clinical disease and to exclude those with clinically increased liver enzymes due to non-metabolic causes[28](#_ENREF_28)) were examined (liver enzymes levels were log-transformed) using linear models. Generally, three sets of models were examined. The first was unadjusted. The second included covariates identified based on a directed acyclic graph (DAG) using the DAGitty program.[29](#_ENREF_29) The same covariates were included in each model: age, sex, race, smoking, alcohol use, education, income, and physical activity. Depending on one’s causal model, adult BMI could be a confounder (if higher genetic propensity to be large leads to higher birthweight and higher adult BMI) or an intermediate (if intrauterine undernutrition leads to later adiposity [30](#_ENREF_30)). In the first case, adjustment would be appropriate; in the second, it could in fact create a spurious association.[31](#_ENREF_31) The final set of models includes the BMI adjustment. Because of substantial missing data for some of the covariates, particularly income (3% for BHS), SES (30% in YF), and physical activity (5% for BHS, 10% for YF), multiple imputation was used (using SAS’s proc mi and proc mianalyze). Finally, interactions with sex was assessed by examining stratified analyses and the product term in multivariable models. For ease of presentation, SGA, LGA, and PTB are presented in the tables; information on LBW and macrosomia is provided in the supplementary material.

As alcohol consumption is a common cause of FLD, a sensitivity analysis excluded heavy drinkers, defined in BHS as daily drinking or drinking 5 or more drinks at one time more than 1x/week in the past month reported at any exam (n=197, 11.0%) and in YF as reporting consuming 6 or more drinks at one time 2 or more times/month (n=736, 23.9%), at any visit. Results were very similar to those shown.

All participants gave informed consent and the BHS study was approved by the Institutional Review Board of Tulane University. The original YF study was approved by the local ethics committees.

**Results**

Participants in both studies were young adults; however, the YF sample was older at the time of measurement, leaner, and had more favorable cardiovascular indicators than the BHS sample (Table 1). All liver enzyme measures were strongly correlated with each other, with BMI, and with lipid measures in both samples (table S1). 391 (15.4%) of the YF sample had indications of fatty liver on ultrasound.

*Bogalusa Heart Study*

For the dichotomous outcomes (table 2), birth measures were not strongly associated with high levels of liver enzymes, although there was a tendency for LGA to be associated with higher GGT (adjusted OR (aOR) 1.58, 95% CI 1.00-2.51; after adjustment for BMI, aOR 1.52, 0.96-2.43) and for SGA to be less likely to have high ALT (fully adjusted aOR 0.31, 95% CI 0.09-1.02). LBW was also associated with a reduced likelihood of being in the high FLI group (aOR 0.53, 0.33-0.85; Table S2).

When liver enzymes were considered as a continuous outcome, some interactions were found between sex and the continuous outcome measures (table 3, S3), so stratified results are provided. When BMI was adjusted for, LBW and PTB were associated with higher AST (among women only) and lower FLI (men only). Macrosomia was associated with lower GGT (women only) in some models.

*Cardiovascular Risk in Young Finns*

For dichotomous outcomes (table 4), the strongest association was with LBW, associated with high GGT (aOR 1.68, 95% CI 1.02-2.76; adjusted for BMI, 1.65, 0.98-2.77) and FLI (1.98, 1.33-2.95) (table 4, S4). For continuous markers (table 5), at least one marker (LBW, PTB, or SGA) was associated with higher GGT (SGA, women only), ALT (men and women), AST (stronger in women; table 5) and higher FLI (women only; table S5). At least one marker of increased growth was associated with lower GGT (stronger in women) and lower ALT (stronger in men). SGA, LBW, and PTB were also associated with increased likelihood of probable fatty liver on ultrasound (table 6).

**Discussion**

The BHS data more strongly supported the idea that some individuals have higher relative weight and metabolic risk throughout their lifetimes: LGA was associated with high GGT, while SGA/LBW was associated with lower ALT and FLI in some analyses. High ALT in early-mid pregnancy was associated with LGA in one study.[32](#_ENREF_32) The YF sample showed results more consistent with the thrifty phenotype hypothesis, with LBW/SGA associated with higher GGT, ALT, and FLI, as well as probable fatty liver on ultrasound. Previous studies have found inverse associations between birthweight and the enzymes studied here, although the exact associations have varied by study.[7](#_ENREF_7), [8](#_ENREF_8), [10](#_ENREF_10), [33](#_ENREF_33) Inverse associations (lower birthweight/higher liver enzymes) have been more commonly found in women,[3](#_ENREF_3), [9](#_ENREF_9), [10](#_ENREF_10) which is mostly consistent with our data for GGT. . The extent to which there are sex differences in developmental programming is unclear, with conflicting results in the relatively few studies available.[34](#_ENREF_34) Several studies have found the association between LBW and type 2 diabetes to be stronger in women,[35](#_ENREF_35) but the association between LBW and hypertension has sometimes been found to be stronger in men.[34](#_ENREF_34) However, birthweight could interact with sex-specific hormone systems; gene expression; diet, alcohol use, or smoking; or growth patterns for differential effects, and animal studies of fetal programming have often found variation by sex.[34](#_ENREF_34), [36](#_ENREF_36)

 We are not aware of another study that has examined PTB as a predictor of later ultrasound fatty liver, although women who enter pregnancy with fatty liver have been found to have a higher risk of PTB.[37](#_ENREF_37) Late PTB was associated with higher ALT, AST, and FLI (though not GGT) values in another study;[12](#_ENREF_12) the majority of the PTB in our study were late, but the mean differences in both of our cohorts are much smaller than found in this previous study Another study found that accelerated weight gain in infancy was associated with FLI but LBW and gestational age were not, but this study was limited to a young adults born preterm.[13](#_ENREF_13)

Support for the hypotheses that both low birthweight and high birthweight are associated with liver fat can be found in the animal literature. Higher-fat diets have been associated with both increased and decreased weight and corresponding adverse effects on the liver.[2](#_ENREF_2), [38-40](#_ENREF_38) Some models[39](#_ENREF_39), [41](#_ENREF_41) indicate differential effects of prenatal diets on fetal outcomes in different strains, which suggests there may be variation by population or genetics. The study populations in this analysis were different in some ways, including race/ethnicity, but no clear risk factor (age, BMI, race) emerged as a cause for the difference. The analyses were repeated within the white portion of the BHS cohort, and results are more similar to black BHS participants than to the Young Finns (data not shown). However, most of the associations had overlapping confidence intervals; the one exception is the opposite-direction associations between LBW/PTB and FLI in the two cohorts. Possible explanations for the difference include measurement error, or genetic, cultural, or life course differences between the populations. If, as has been suggested in some studies,[13](#_ENREF_13), [42](#_ENREF_42) catch-up growth is a stronger predictor of adult metabolic health than birthweight per se, it is possible that the postnatal growth patterns differ between the two cohorts.

Strengths of the study include the fairly large sample size and the ability to assess the study question in two different cohorts. This analysis incorporates large studies of young adults and includes a diverse, U.S-based population, unlike previous research.[3](#_ENREF_3), [4](#_ENREF_4), [9](#_ENREF_9), [10](#_ENREF_10) Limitations include the lack of a direct assessment of some relevant covariates, such as liver fat concentrations, body fat mass and distribution, diet, and substance use, and the lack of standardization of the timing of the measures. A single outcome measure was used; liver enzymes have substantial variability and are raised in a number of clinical conditions.[43](#_ENREF_43) We cannot take into account hepatosteatosis due to hepatotoxic medication, and only a limited adjustment can be made for alcohol use (based on self-report), although a sensitivity analysis showed excluding heavy drinkers had little effect on the results (data not shown). Ultrasound is not a direct measurement of liver fat, although the echogenicity of the liver is an indicator of probable fatty deposition, and is used by most general medicine doctors. A large number of comparisons were made, so type 1 error is a possibility, particularly for interaction analyses. As in any study of birth outcomes and adult cardiovascular parameters, no mechanism can be directly demonstrated, and the possibility of unmeasured confounders is always a possibility. We do not have information on the specific causes of growth restriction or preterm birth, and so cannot distinguish between possible causes such as placental dysfunction and infection[44](#_ENREF_44). Pre-eclampsia is a cause of many medically-indicated preterm births, and has been associated with many later metabolic changes.[45](#_ENREF_45) Although adult adiposity can directly cause FLD, birthweight would not be a direct cause, and so the relationship would reflect an underlying nutritional, genetic, or growth link between the two.

These results contribute to the literature on the relationship between birthweight and adult FLD, suggesting a physiological link between these characteristics. This analysis adds to the growing body of research suggesting intrauterine influences on adult cardiovascular health. It also, however, encourages consideration of population and genetic variation in these relationships.

**Acknowledgements and Financial Support**

The Bogalusa Heart Study is supported by NIH grants R01HL02942, HL15103, HL15103, HD32194, AG16592

The Young Finns Study has been financially supported by the Academy of Finland (grants 126925, 121584, 124282, 129378 (Salve), 117787 (Gendi), and 41071 (Skidi)); the Social Insurance Institution of Finland; Kuopio, Tampere and Turku University Hospital Medical Funds; Juho Vainio Foundation; Paavo Nurmi Foundation; Finnish Foundation of Cardiovascular Research; Finnish Cultural Foundation; and Yrjö Jahnsson Foundation.

**Conflicts of Interests**

None

**Ethical standards**

The authors assert that all procedures contributing to this work comply with the ethical standards of the United States and Finland and with the Helsinki Declaration of 1975, as revised in 2008. All participants gave informed consent and the BHS study was approved by the Institutional Review Board of Tulane University. The original YF study was approved by the local ethics committees.

**References**

1. Cottrell EC, Ozanne SE. Developmental programming of energy balance and the metabolic syndrome. *Proc Nutr Soc*. 2007;66(2), 198-206.

2. Elahi MM, Cagampang FR, Mukhtar D, Anthony FW, Ohri SK, Hanson MA. Long-term maternal high-fat feeding from weaning through pregnancy and lactation predisposes offspring to hypertension, raised plasma lipids and fatty liver in mice. *Br J Nutr*. 2009;102(4), 514-519.

3. Sandboge S, Perala MM, Salonen MK, et al. Early growth and non-alcoholic fatty liver disease in adulthood-the NAFLD liver fat score and equation applied on the Helsinki Birth Cohort Study. *Ann Med*. 2013;45(5-6), 430-437.

4. Fraser A, Ebrahim S, Davey Smith G, Lawlor DA. The associations between height components (leg and trunk length) and adult levels of liver enzymes. *J Epidemiol Community Health*. 2008;62(1), 48-53.

5. Xia MF, Yan HM, Lin HD, et al. Elevation of liver enzymes within the normal limits and metabolic syndrome. *Clin Exp Pharmacol Physiol*. 2011;38(6), 373-379.

6. Nobili V, Marcellini M, Marchesini G, et al. Intrauterine growth retardation, insulin resistance, and nonalcoholic fatty liver disease in children. *Diabetes Care*. 2007;30(10), 2638-2640.

7. Anderson EL, Howe LD, Fraser A, et al. Weight trajectories through infancy and childhood and risk of non-alcoholic fatty liver disease in adolescence: The ALSPAC study. *J Hepatol*. 2014; doi: 10.1016/j.jhep.2014.04.018.

8. Robertson T, Benzeval M. Do mismatches between pre- and post-natal environments influence adult physiological functioning? *PloS ONE*. 2014;9(1), e86953.

9. Fraser A, Ebrahim S, Ben-Shlomo Y, Davey Smith G, Lawlor DA. Intrauterine growth retardation, insulin resistance, and nonalcoholic fatty liver disease in children: response to Nobili et al. *Diabetes Care*. 2007;30(11), e124; author reply e125.

10. Fraser A, Ebrahim S, Smith GD, Lawlor DA. The associations between birthweight and adult markers of liver damage and function. *Paediatr Perinat Epidemiol*. 2008;22(1), 12-21.

11. Bedogni G, Bellentani S, Miglioli L, et al. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. *BMC Gastroenterol*. 2006;6, 33.

12. Sipola-Leppanen M, Vaarasmaki M, Tikanmaki M, et al. Cardiometabolic risk factors in young adults who were born preterm. *Am J Epidemiol*. 2015;181(11), 861-873.

13. Breij LM, Kerkhof GF, Hokken-Koelega AC. Risk for Nonalcoholic Fatty Liver Disease in Young Adults Born Preterm. *Hormone research in paediatrics*. 2015;84(3), 199-205.

14. Luo ZC, Xiao L, Nuyt AM. Mechanisms of developmental programming of the metabolic syndrome and related disorders. *World J Diabetes*. 2010;1(3), 89-98.

15. Simmons R. Developmental origins of adult metabolic disease: concepts and controversies. *Trends Endocrinol Metab*. 2005;16(8), 390-394.

16. Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia*. 1992;35(7), 595-601.

17. Raitakari OT, Juonala M, Ronnemaa T, et al. Cohort profile: The Cardiovascular Risk in Young Finns Study. *Int J Epidemiol*. 2008;37(6), 1220-1226.

18. Mzayek F, Hassig S, Sherwin R, et al. The association of birth weight with developmental trends in blood pressure from childhood through mid-adulthood: The Bogalusa Heart Study. *Am J Epidemiol*. 2007;166(4), 413-420.

19. Sou SC, Chen WJ, Hsieh WS, Jeng SF. Severe obstetric complications and birth characteristics in preterm or term delivery were accurately recalled by mothers. *J Clin Epidemiol*. 2006;59(4), 429-435.

20. Jaspers M, de Meer G, Verhulst FC, Ormel J, Reijneveld SA. Limited validity of parental recall on pregnancy, birth, and early childhood at child age 10 years. *J Clin Epidemiol*. 2010;63(2), 185-191.

21. Adegboye AR, Heitmann B. Accuracy and correlates of maternal recall of birthweight and gestational age. *BJOG*. 2008;115(7), 886-893.

22. Hakim RB, Tielsch JM, See LC. Agreement between maternal interview- and medical record-based gestational age. *Am J Epidemiol*. 1992;136(5), 566-573.

23. Edens MA, van Ooijen PM, Post WJ, et al. Ultrasonography to quantify hepatic fat content: validation by 1H magnetic resonance spectroscopy. *Obesity (Silver Spring, Md)*. 2009;17(12), 2239-2244.

24. Saverymuttu SH, Joseph AE, Maxwell JD. Ultrasound scanning in the detection of hepatic fibrosis and steatosis. *Br Med J (Clin Res Ed)*. 1986;292(6512), 13-15.

25. Suomela E, Oikonen M, Virtanen J, et al. Prevalence and determinants of fatty liver in normal-weight and overweight young adults. The Cardiovascular Risk in Young Finns Study. *Ann Med*. 2015;47(1), 40-46.

26. Raitakari OT, Porkka KV, Taimela S, Telama R, Rasanen L, Viikari JS. Effects of persistent physical activity and inactivity on coronary risk factors in children and young adults. The Cardiovascular Risk in Young Finns Study. *Am J Epidemiol*. 1994;140(3), 195-205.

27. Ceriotti F, Henny J, Queralto J, et al. Common reference intervals for aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT) in serum: results from an IFCC multicenter study. *Clin Chem Lab Med*. 2010;48(11), 1593-1601.

28. Patel DA, Srinivasan SR, Xu JH, Chen W, Berenson GS. Persistent elevation of liver function enzymes within the reference range is associated with increased cardiovascular risk in young adults: the Bogalusa Heart Study. *Metabolism*. 2007;56(6), 792-798.

29. Textor J, Hardt J, Knuppel S. DAGitty: a graphical tool for analyzing causal diagrams. *Epidemiology*. 2011;22(5), 745.

30. Ong KK, Dunger DB. Perinatal growth failure: the road to obesity, insulin resistance and cardiovascular disease in adults. *Best Pract Res Clin Endocrinol Metab*. 2002;16(2), 191-207.

31. Tu YK, West R, Ellison GT, Gilthorpe MS. Why evidence for the fetal origins of adult disease might be a statistical artifact: the "reversal paradox" for the relation between birth weight and blood pressure in later life. *Am J Epidemiol*. 2005;161(1), 27-32.

32. Yarrington CD, Cantonwine DE, Seely EW, McElrath TF, Zera CA. The association of early unexplained elevated alanine aminotransferase with large for gestational age birth weight. *Am J Obstet Gynecol*. 2016; doi: 10.1016/j.ajog.2016.04.051.

33. Cai G, Cole SA, Haack K, Butte NF, Comuzzie AG. Bivariate linkage confirms genetic contribution to fetal origins of childhood growth and cardiovascular disease risk in Hispanic children. *Hum Genet*. 2007;121(6), 737-744.

34. Dasinger JH, Alexander BT. Gender differences in developmental programming of cardiovascular diseases. *Clinical science (London, England : 1979)*. 2016;130(5), 337-348.

35. Alexander BT, Henry Dasinger J, Intapad S. Effect of low birth weight on women's health. *Clin Ther*. 2014;36(12), 1913-1923.

36. Gilbert JS, Nijland MJ. Sex differences in the developmental origins of hypertension and cardiorenal disease. *American journal of physiology Regulatory, integrative and comparative physiology*. 2008;295(6), R1941-1952.

37. Hagstrom H, Hoijer J, Ludvigsson JF, et al. Adverse outcomes of pregnancy in women with non-alcoholic fatty liver disease. *Liver Int*. 2015; doi: 10.1111/liv.12902.

38. Aagaard-Tillery KM, Grove K, Bishop J, et al. Developmental origins of disease and determinants of chromatin structure: maternal diet modifies the primate fetal epigenome. *J Mol Endocrinol*. 2008;41(2), 91-102.

39. McCurdy CE, Bishop JM, Williams SM, et al. Maternal high-fat diet triggers lipotoxicity in the fetal livers of nonhuman primates. *J Clin Invest*. 2009;119(2), 323-335.

40. Dudley KJ, Sloboda DM, Connor KL, Beltrand J, Vickers MH. Offspring of mothers fed a high fat diet display hepatic cell cycle inhibition and associated changes in gene expression and DNA methylation. *PloS ONE*. 2011;6(7), e21662.

41. Knight BS, Pennell CE, Shah R, Lye SJ. Strain differences in the impact of dietary restriction on fetal growth and pregnancy in mice. *Reprod Sci*. 2007;14(1), 81-90.

42. Morrison JL, Duffield JA, Muhlhausler BS, Gentili S, McMillen IC. Fetal growth restriction, catch-up growth and the early origins of insulin resistance and visceral obesity. *Pediatric nephrology (Berlin, Germany)*. 2010;25(4), 669-677.

43. Friedman LS. Approach to the patient with abnormal liver biochemical and function tests. In UpToDate. (ed. Chopra S), 2015. UpToDate: Waltham, MA.

44. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet*. 2008;371(9606), 75-84.

45. Adams T, Yeh C, Bennett-Kunzier N, Kinzler WL. Long-term maternal morbidity and mortality associated with ischemic placental disease. *Semin Perinatol*. 2014;38(3), 146-150.

|  |
| --- |
| Table 1. Participants in the Bogalusa Heart Study, 1995-2002 (n=1803) and Cardiovascular Risk in Young Finns study (2001-2011, n=3571)  |
|  |  | Bogalusa Heart Study |
|  |  | N | % |  |  |  |
| Age at oldest visit |  |  |  |  |  |  |
| 18-<20 |  | 40 | 2.2 |  |  |  |
| 20-<30 |  | 590 | 32.7 |  |  |  |
| 30-<40 |  | 933 | 51.8 |  |  |  |
| 40+ |  | 240 | 13.3 |  |  |  |
|  |  |  |  |  |  |  |
| Sex |  |  |  |  |  |  |
| Male |  | 794 | 44.0 |  |  |  |
| Female |  | 1009 | 56.0 |  |  |  |
|  |  |  |  |  |  |  |
| Race |  |  |  |  |  |  |
| Black |  | 556 | 30.8 |  |  |  |
| White |  | 1247 | 69.2 |  |  |  |
|  |  |  |  |  |  |  |
| BMI category |  |  |  |  |  |  |
| <20 |  | 126 | 7.0 |  |  |  |
| 20-<25 |  | 525 | 29.2 |  |  |  |
| 25-<30 |  | 516 | 28.7 |  |  |  |
| 30+ |  | 632 | 35.1 |  |  |  |
|  |  |  |  |  |  |  |
| Smoking history |  |  |  |  |  |  |
| never |  | 942 | 55.8 |  |  |  |
| former |  | 179 | 10.6 |  |  |  |
| 1-15 cigarettes/day |  | 319 | 18.9 |  |  |  |
| >15 cigarettes/day |  | 249 | 14.7 |  |  |  |
|  |  |  |  |  |  |  |
| income |  |  |  |  |  |  |
| <$15K |  | 554 | 31.8 |  |  |  |
| $15K-$30K |  | 409 | 23.5 |  |  |  |
| >$30K-$45K |  | 280 | 16.1 |  |  |  |
| >$45K |  | 501 | 28.7 |  |  |  |
|  |  |  |  |  |  |  |
| physical activity (combined work and nonwork) |  |  |  |
| low activity |  | 243 | 14.2 |  |  |  |
| medium |  | 289 | 16.9 |  |  |  |
| high |  | 614 | 35.9 |  |  |  |
| very active |  | 565 | 33.0 |  |  |  |
|  |  |  |  |  |  |  |
| alcohol use (in yr of enzyme measure) |  |  |  |  |  |  |
| do not drink |  | 1076 | 60.5 |  |  |  |
| drink regularly |  | 703 | 39.5 |  |  |  |
|  |  |  |  |  |  |  |
| Less than 1x week |  | 205 | 11.5 |  |  |  |
| 1-2x week |  | 296 | 16.6 |  |  |  |
| 3-4x week |  | 104 | 5.9 |  |  |  |
| Daily or almost daily |  | 98 | 5.5 |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| preterm birth |  | 97 | 6.1 |  |  |  |
|  |  |  |  |  |  |  |
| low birthweight |  | 114 | 6.3 |  |  |  |
|  |  |  |  |  |  |  |
| small-for-gestational-age |  | 125 | 7.9 |  |  |  |
| large-for-gestational-age |  | 158 | 10.0 |  |  |  |
|  |  |  |  |  |  |  |
|  |  | mean | median | SD | min | max |
| GGT† (U/L) |  | 35.3 | 22.0 | 53.4 | 3.0 | 750.0 |
| ALT (U/L) |  | 23.9 | 18.0 | 20.9 | 3.0 | 293.0 |
| AST (U/L) |  | 23.8 | 20.0 | 17.7 | 5.0 | 385.0 |
| FLI‡ |  | 43.6 | 35.0 | 34.3 | 0.5 | 100.0 |
|  |  |  |  |  |  |  |
| BMI (kg/m2) |  | 28.5 | 27.2 | 7.1 | 15.2 | 62.0 |
| Triglycerides (mg/dL) |  | 120.9 | 95.0 | 99.7 | 23.0 | 1463.0 |
| †at oldest visit |  |  |  |  |  |  |
| ‡ FLI = (e 0.953\*ln(triglycerides) + 0.139\*BMI + 0.718\*ln(ggt) +0.053\*waist circumference - 15.745) / (1 + e 0.953\*ln (triglycerides) +0.139\*BMI + 0.718\*loge (ggt) + 0.053\*waist circumference - 15.745) \* 100 |

|  |
| --- |
| Table 1, cont.  |
| Young Finns Study |  |  |  |  |  |
|  |  | N | % |  |  |  |
| Age at oldest visit |  |  |  |  |  |  |
| 18-<20 |  | 0 |  |  |  |  |
| 20-<30 |  | 157 | 4.5 |  |  |  |
| 30-<40 |  | 1401 | 40.4 |  |  |  |
| 40+ |  | 1913 | 55.1 |  |  |  |
|  |  |  |  |  |  |  |
| Sex |  |  |  |  |  |  |
| Male |  | 1082 | 31.2 |  |  |  |
| Female |  | 2389 | 68.8 |  |  |  |
|  |  |  |  |  |  |  |
| Race |  |  |  |  |  |  |
| Black |  | ‡ |  |  |  |  |
| White |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| BMI category |  |  |  |  |  |  |
| <20 |  | 196 | 5.7 |  |  |  |
| 20-<25 |  | 1347 | 39.3 |  |  |  |
| 25-<30 |  | 1207 | 35.2 |  |  |  |
| 30+ |  | 676 | 19.7 |  |  |  |
|  |  |  |  |  |  |  |
| Smoking history |  |  |  |  |  |  |
| never |  | 1692 | 51.1 |  |  |  |
| former |  | 779 | 23.5 |  |  |  |
| current |  | 838 | 25.3 |  |  |  |
|  |  |  |  |  |  |  |
| SES in 2007 (based on occupation) |  |  |  |  |
| manual |  | 847 | 34.0 |  |  |  |
| lower non-manual |  | 499 | 20.0 |  |  |  |
| upper non-manual |  | 1144 | 45.9 |  |  |  |
|  |  |  |  |  |  |  |
| physical activity (nonwork) |  |  |  |
| low activity |  | 286 | 9.0 |  |  |  |
| medium |  | 853 | 26.8 |  |  |  |
| high |  | 1342 | 42.1 |  |  |  |
| very active |  | 706 | 22.2 |  |  |  |
|  |  |  |  |  |  |  |
| alcohol intake (avg drinks/day) at liver enzyme visit |  |  |
| 0 |  | 944 | 28.7 |  |  |  |
| <=1 |  | 1668 | 50.7 |  |  |  |
| >1-2 |  | 410 | 12.5 |  |  |  |
| >2 |  | 266 | 8.1 |  |  |  |
|  |  |  |  |  |  |  |
| preterm birth |  | 141 | 4.1 |  |  |  |
|  |  |  |  |  |  |  |
| low birthweight |  | 116 | 3.3 |  |  |  |
|  |  |  |  |  |  |  |
| small-for-gestational-age |  | 346 | 10.0 |  |  |  |
| large-for-gestational-age |  | 335 | 9.7 |  |  |  |
|  |  |  |  |  |  |  |
|  |  | mean | median | SD | min | max |
| GGT\* (U/L) |  | 29.1 | 20.0 | 33.3 | 5.0 | 562 |
| ALT (U/L) |  | 15.6 | 12.0 | 12.8 | 2.0 | 253 |
| AST (U/L) |  | 22.1 | 12.0 | 12.0 | 10.0 | 208 |
| FLI§ |  | 36.7 | 25.1 | 30.5 | 1.2 | 100 |
|  |  |  |  |  |  |  |
| BMI (kg/m2) |  | 26.3 | 25.5 | 5.1 | 16.2 | 58.5 |
| triglycerides (mg/dL) |  | 115.0 | 97.3 | 88.5 | 26.6 | 3006.2 |
| †at oldest visit |  |  |  |  |  |  |
| ‡ race/ethnicity information was not collected as such in the Young Finns study; however, the vast majority is white |
| § FLI = (e 0.953\*ln(triglycerides) + 0.139\*BMI + 0.718\*ln(ggt) +0.053\*waist circumference - 15.745) / (1 + e 0.953\*ln (triglycerides) +0.139\*BMI + 0.718\*loge (ggt) + 0.053\*waist circumference - 15.745) \* 100 |

|  |
| --- |
| Table 2. Birth outcomes as predictors of clinically high levels of liver enzymes, The Bogalusa Heart Study (n=1803) |
|  |  | unadjusted |  | adjusted for age, sex, race, smoking, alcohol use, education, income, physical activity |  | adjusted for previous + BMI |
|  |  | OR† | 95% CI |  | OR | 95% CI |  | OR | 95% CI |
| gamma-glutamate transferase (GGT) |  |  |  |  |  |  |  |  |  |
| small-for-gestational-age |  | 1.25 | (0.76, 2.07) |  | 0.91 | (0.53, 1.55) |  | 0.96 | (0.56, 1.64) |
| large-for-gestational-age |  | 1.45 | (0.94, 2.24) |  | 1.58 | (1.00, 2.51) |  | 1.52 | (0.96, 2.43) |
| preterm birth |  | 1.22 | (0.69, 2.17) |  | 1.17 | (0.64, 2.15) |  | 1.20 | (0.65, 2.21) |
|  |  |  |  |  |  |  |  |  |  |
| alanine transaminase (ALT) |  |  |  |  |  |  |  |  |  |
| small-for-gestational-age |  | 0.31 | (0.10, 1.00) |  | 0.32 | (0.10, 1.03) |  | 0.31 | (0.09, 1.02) |
| large-for-gestational-age |  | 1.01 | (0.53, 1.92) |  | 0.94 | (0.48, 1.84) |  | 0.88 | (0.45, 1.73) |
| preterm birth |  | 1.58 | (0.80, 3.14) |  | 1.48 | (0.72, 3.03) |  | 1.52 | (0.73, 3.15) |
|  |  |  |  |  |  |  |  |  |  |
| aspartate transaminase (AST) |  |  |  |  |  |  |  |  |  |
| small-for-gestational-age |  | 0.67 | (0.34, 1.30) |  | 0.48 | (0.24, 0.99) |  | 0.50 | (0.24, 1.01) |
| large-for-gestational-age |  | 1.09 | (0.66, 1.81) |  | 1.12 | (0.65, 1.92) |  | 1.09 | (0.64, 1.88) |
| preterm birth |  | 1.39 | (0.77, 2.51) |  | 1.13 | (0.60, 2.15) |  | 1.14 | (0.60, 2.17) |
|  |  |  |  |  |  |  |  |  |  |
| fatty liver index (FLI)‡ |  |  |  |  |  |  |  |  |  |
| small-for-gestational-age |  | 0.77 | (0.52, 1.14) |  | 0.71 | (0.47, 1.08) |  | Measurement includes BMI |
| large-for-gestational-age |  | 1.15 | (0.82, 1.61) |  | 1.25 | (0.88, 1.79) |  |  |  |
| preterm birth |  | 0.75 | (0.48, 1.16) |  | 0.75 | (0.47, 1.21) |  |  |  |
| † Reference category for all models is all participants not categorized as “case”. Cut-offs for clinical concern: for men, GGT>68 U/L, ALT>59 U/L; for women, GGT>40 U/L, ALT>41 U/L [27](#_ENREF_27" \o "Ceriotti, 2010 #423); for all, AST>34 U/L, FLI>=60 [11](#_ENREF_11).  |
| ‡ FLI = (e 0.953\*ln(triglycerides) + 0.139\*BMI + 0.718\*ln(ggt) +0.053\*waist circumference - 15.745) / (1 + e 0.953\*ln (triglycerides) +0.139\*BMI + 0.718\*loge (ggt) + 0.053\*waist circumference - 15.745) \* 100 |
|  |

|  |
| --- |
| Table 3. Birth outcomes as predictors of continuous liver enzymes (log-transformed, within the normal range), with adjustment for confounders, the Bogalusa Heart Study  |
|  |  | model 1 |  |  |  | model 2 |  |  |
|  |  | unadjusted |  |  |  | adjusted for age, sex, race, smoking, alcohol use, education, income, physical activity |  |  |
|  |  | beta† | SE | p |  | p for interaction |  | beta | SE | p |  | p for interaction |
| gamma-glutamate transferase (GGT) |  |  |  |  |  |  |  |  |  |  |  |  |
| men |  |  |  |  |  |  |  |  |  |  |  |  |
| small-for-gestational-age |  | 0.01 | 0.07 | 0.89 |  | 0.19 |  | -0.05 | 0.07 | 0.47 |  | 0.13 |
| large-for-gestational-age |  | -0.01 | 0.06 | 0.82 |  | 0.46 |  | 0.02 | 0.06 | 0.79 |  | 0.46 |
| preterm birth |  | -0.04 | 0.08 | 0.62 |  | 0.17 |  | -0.05 | 0.08 | 0.48 |  | 0.08 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| women |  |  |  |  |  |  |  |  |  |  |  |  |
| small-for-gestational-age |  | 0.12 | 0.05 | 0.01 |  |  |  | 0.07 | 0.05 | 0.14 |  |  |
| large-for-gestational-age |  | -0.07 | 0.05 | 0.15 |  |  |  | -0.04 | 0.05 | 0.41 |  |  |
| preterm birth |  | 0.09 | 0.06 | 0.12 |  |  |  | 0.09 | 0.06 | 0.13 |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| alanine transaminase (ALT) |  |  |  |  |  |  |  |  |  |  |  |  |
| men |  |  |  |  |  |  |  |  |  |  |  |  |
| small-for-gestational-age |  | -0.02 | 0.07 | 0.76 |  | 0.69 |  | -0.02 | 0.07 | 0.79 |  | 0.67 |
| large-for-gestational-age |  | 0.02 | 0.06 | 0.68 |  | 0.59 |  | 0.02 | 0.06 | 0.76 |  | 0.74 |
| preterm birth |  | -0.07 | 0.07 | 0.37 |  | 0.28 |  | -0.01 | 0.07 | 0.93 |  | 0.21 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| women |  |  |  |  |  |  |  |  |  |  |  |  |
| small-for-gestational-age |  | 0.01 | 0.05 | 0.81 |  |  |  | 0.02 | 0.05 | 0.62 |  |  |
| large-for-gestational-age |  | 0.06 | 0.05 | 0.19 |  |  |  | 0.04 | 0.05 | 0.45 |  |  |
| preterm birth |  | 0.04 | 0.06 | 0.55 |  |  |  | 0.09 | 0.06 | 0.13 |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| aspartate transaminase (AST) |  |  |  |  |  |  |  |  |  |  |  |  |
| men |  |  |  |  |  |  |  |  |  |  |  |  |
| small-for-gestational-age |  | 0.00 | 0.04 | 0.92 |  | 0.54 |  | 0.00 | 0.04 | 0.99 |  | 0.53 |
| large-for-gestational-age |  | -0.04 | 0.03 | 0.23 |  | 0.60 |  | -0.04 | 0.03 | 0.22 |  | 0.59 |
| preterm birth |  | 0.01 | 0.04 | 0.87 |  | 0.06 |  | 0.00 | 0.04 | 0.96 |  | 0.06 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| women |  |  |  |  |  |  |  |  |  |  |  |  |
| small-for-gestational-age |  | 0.03 | 0.03 | 0.26 |  |  |  | 0.04 | 0.03 | 0.22 |  |  |
| large-for-gestational-age |  | -0.01 | 0.03 | 0.62 |  |  |  | -0.03 | 0.03 | 0.38 |  |  |
| preterm birth |  | 0.11 | 0.04 | <0.01 |  |  |  | 0.11 | 0.04 | <0.01 |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| fatty liver index (FLI)‡ |  |  |  |  |  |  |  |  |  |  |  |  |
| men |  |  |  |  |  |  |  |  |  |  |  |  |
| small-for-gestational-age |  | -10.49 | 4.93 | 0.03 |  | 0.09 |  | -8.44 | 4.87 | 0.08 |  | 0.13 |
| large-for-gestational-age |  | 3.44 | 4.00 | 0.39 |  | 0.53 |  | 2.88 | 3.85 | 0.45 |  | 0.52 |
| preterm birth |  | -12.60 | 5.13 | 0.01 |  | 0.03 |  | -6.74 | 5.04 | 0.18 |  | 0.07 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| women |  |  |  |  |  |  |  |  |  |  |  |  |
| small-for-gestational-age |  | 0.50 | 4.01 | 0.90 |  |  |  | -4.24 | 3.90 | 0.28 |  |  |
| large-for-gestational-age |  | -0.09 | 3.90 | 0.98 |  |  |  | 3.69 | 3.78 | 0.33 |  |  |
| preterm birth |  | 2.70 | 4.76 | 0.57 |  |  |  | -0.41 | 4.76 | 0.93 |  |  |
| † increase in outcome in those with and without the listed birth outcome |
| ‡ not log-transformed |  |  |  |  |  |  |  |  |  |  |  |  |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | model 3 |  |  |
|  |  | previous + BMI |  |  |
|  |  | beta | SE | p |  | p for interaction |
| gamma-glutamate transferase (GGT) |  |  |  |  |  |  |
| men |  |  |  |  |  |  |
| small-for-gestational-age |  | -0.05 | 0.07 | 0.46 |  | 0.15 |
| large-for-gestational-age |  | 0.01 | 0.06 | 0.84 |  | 0.51 |
| preterm birth |  | -0.05 | 0.07 | 0.47 |  | 0.07 |
|  |  |  |  |  |  |  |
| women |  |  |  |  |  |  |
| small-for-gestational-age |  | 0.08 | 0.05 | 0.08 |  |  |
| large-for-gestational-age |  | -0.05 | 0.05 | 0.29 |  |  |
| preterm birth |  | 0.11 | 0.06 | 0.07 |  |  |
|  |  |  |  |  |  |  |
| alanine transaminase (ALT) |  |  |  |  |  |  |
| men |  |  |  |  |  |  |
| small-for-gestational-age |  | -0.03 | 0.07 | 0.69 |  | 0.62 |
| large-for-gestational-age |  | 0.01 | 0.05 | 0.85 |  | 0.85 |
| preterm birth |  | 0.00 | 0.07 | 0.98 |  | 0.23 |
|  |  |  |  |  |  |  |
| women |  |  |  |  |  |  |
| small-for-gestational-age |  | 0.04 | 0.05 | 0.41 |  |  |
| large-for-gestational-age |  | 0.01 | 0.05 | 0.79 |  |  |
| preterm birth |  | 0.11 | 0.06 | 0.08 |  |  |
|  |  |  |  |  |  |  |
| aspartate transaminase (AST) |  |  |  |  |  |  |
| men |  |  |  |  |  |  |
| small-for-gestational-age |  | 0.00 | 0.04 | 0.96 |  | 0.50 |
| large-for-gestational-age |  | -0.04 | 0.03 | 0.21 |  | 0.58 |
| preterm birth |  | 0.00 | 0.04 | 0.94 |  | 0.06 |
|  |  |  |  |  |  |  |
| women |  |  |  |  |  |  |
| small-for-gestational-age |  | 0.04 | 0.03 | 0.18 |  |  |
| large-for-gestational-age |  | -0.03 | 0.03 | 0.35 |  |  |
| preterm birth |  | 0.11 | 0.04 | <0.01 |  |  |
|  |  |  |  |  |  |  |
| fatty liver index (FLI) |  |  |  |  |  |  |
|  |  | BMI included in measure |  |  |

|  |
| --- |
| Table 4. Birth outcomes as predictors of clinically high levels of liver enzymes, Cardiovascular Risk in Young Finns Study (n=3571) |
|  |  | unadjusted |  | adjusted for age, sex, smoking, alcohol use, social class, physical activity |  | adjusted for previous + BMI |
|  |  | OR | 95% CI |  | OR | 95% CI |  | OR | 95% CI |
| gamma-glutamate transferase (GGT) |  |  |  |  |  |  |  |  |  |
| small-for-gestational-age |  | 1.24 | (0.89, 1.74) |  | 1.15 | (0.82, 1.63) |  | 1.23 | (0.86, 1.75) |
| large-for-gestational-age |  | 1.29 | (0.92, 1.80) |  | 1.35 | (0.96, 1.91) |  | 1.28 | (0.89, 1.85) |
| preterm birth |  | 1.22 | (0.74, 2.03) |  | 1.21 | (0.72, 2.04) |  | 1.17 | (0.68, 2.01) |
|  |  |  |  |  |  |  |  |  |  |
| alanine transaminase (ALT) |  |  |  |  |  |  |  |  |  |
| small-for-gestational-age |  | 0.82 | (0.33, 2.06) |  | 0.77 | (0.30, 1.96) |  | 0.83 | (0.32, 2.11) |
| large-for-gestational-age |  | 1.45 | (0.68, 3.08) |  | 1.46 | (0.70, 3.15) |  | 1.37 | (0.63, 2.98) |
| preterm birth |  | 1.71 | (0.61, 4.78) |  | 1.58 | (0.55, 4.50) |  | 1.50 | (0.50, 4.45) |
|  |  |  |  |  |  |  |  |  |  |
| aspartate transaminase (AST) |  |  |  |  |  |  |  |  |  |
| small-for-gestational-age |  | 0.82 | (0.33, 2.06) |  | 0.77 | (0.30, 1.96) |  | 0.83 | (0.32, 2.11) |
| large-for-gestational-age |  | 1.45 | (0.68, 3.08) |  | 1.46 | (0.70, 3.15) |  | 1.37 | (0.63, 2.98) |
| preterm birth |  | 1.71 | (0.61, 4.78) |  | 1.58 | (0.55, 4.50) |  | 1.50 | (0.50, 4.45) |
|  |  |  |  |  |  |  |  |  |  |
| fatty liver index (FLI) |  |  |  |  |  |  |  |  |  |
| small-for-gestational-age |  | 1.17 | (0.89, 1.55) |  | 1.13 | (0.87, 1.47) |  | Measurement includes BMI |
| large-for-gestational-age |  | 1.06 | (0.80, 1.41) |  | 0.97 | (0.74, 1.28) |  |  |  |
| preterm birth |  | 1.31 | (0.88, 1.96) |  | 1.36 | (0.92, 2.02) |  |  |  |
| † Reference category for all models is all participants not categorized as “case”. Cut-offs for clinical concern: for men, GGT>68, ALT>59; for women, GGT>40, ALT>41 [27](#_ENREF_27); for all, AST>34, FLI>=60 [11](#_ENREF_11).  |

|  |
| --- |
| Table 5. Birth outcomes as predictors of continuous liver enzymes (log-transformed, within the normal range), Cardiovascular Risk in Young Finns Study  |
|  |  | model 1 |  |  |  | model 2 |  |  |
|  |  | unadjusted |  |  |  | adjusted for age, sex, race, smoking, alcohol use, education, income, physical activity |  |  |
|  |  | betaa | SE | p |  | p for interaction |  | beta | SE | p |  | p for interaction |
| gamma-glutamate transferase (GGT) |  |  |  |  |  |  |  |  |  |  |  |  |
| men |  |  |  |  |  |  |  |  |  |  |  |  |
| small-for-gestational-age |  | 0.01 | 0.05 | 0.79 |  | 0.19 |  | 0.00 | 0.05 | 0.96 |  | 0.08 |
| large-for-gestational-age |  | -0.03 | 0.05 | 0.61 |  | 0.64 |  | -0.02 | 0.05 | 0.66 |  | 0.46 |
| preterm birth |  | 0.13 | 0.08 | 0.09 |  | 0.02 |  | 0.10 | 0.07 | 0.18 |  | 0.04 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| women |  |  |  |  |  |  |  |  |  |  |  |  |
| small-for-gestational-age |  | 0.08 | 0.00 | <0.01 |  |  |  | 0.09 | 0.03 | <0.01 |  |  |
| large-for-gestational-age |  | -0.05 | 0.03 | 0.06 |  |  |  | -0.06 | 0.03 | 0.03 |  |  |
| preterm birth |  | -0.06 | 0.04 | 0.15 |  |  |  | -0.06 | 0.04 | 0.17 |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| alanine transaminase (ALT) |  |  |  |  |  |  |  |  |  |  |  |  |
| men |  |  |  |  |  |  |  |  |  |  |  |  |
| small-for-gestational-age |  | 0.06 | 0.05 | 0.22 |  | 0.91 |  | 0.04 | 0.05 | 0.38 |  | 0.98 |
| large-for-gestational-age |  | -0.01 | 0.05 | 0.80 |  | 0.78 |  | -0.01 | 0.05 | 0.82 |  | 0.77 |
| preterm birth |  | 0.15 | 0.07 | 0.03 |  | <0.01 |  | 0.14 | 0.07 | 0.05 |  | <0.01 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| women |  |  |  |  |  |  |  |  |  |  |  |  |
| small-for-gestational-age |  | 0.05 | 0.03 | 0.06 |  |  |  | 0.05 | 0.03 | 0.09 |  |  |
| large-for-gestational-age |  | 0.00 | 0.03 | 0.93 |  |  |  | 0.01 | 0.03 | 0.71 |  |  |
| preterm birth |  | -0.07 | 0.04 | 0.10 |  |  |  | -0.06 | 0.04 | 0.13 |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| aspartate transaminase (AST)  |  |  |  |  |  |  |  |  |  |  |  |  |
| men |  |  |  |  |  |  |  |  |  |  |  |  |
| small-for-gestational-age |  | 0.02 | 0.02 | 0.36 |  | 0.37 |  | 0.02 | 0.02 | 0.38 |  | 0.32 |
| large-for-gestational-age |  | -0.01 | 0.03 | 0.80 |  | 0.42 |  | -0.03 | 0.03 | 0.26 |  | 0.22 |
| preterm birth |  | 0.07 | 0.04 | 0.06 |  | 0.27 |  | -0.01 | 0.03 | 0.65 |  | 0.22 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| women |  |  |  |  |  |  |  |  |  |  |  |  |
| small-for-gestational-age |  | 0.05 | 0.02 | <0.01 |  |  |  | 0.05 | 0.02 | <0.01 |  |  |
| large-for-gestational-age |  | 0.02 | 0.02 | 0.26 |  |  |  | 0.02 | 0.02 | 0.23 |  |  |
| preterm birth |  | 0.02 | 0.03 | 0.51 |  |  |  | 0.01 | 0.03 | 0.69 |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| fatty liver index (FLI)† |  |  |  |  |  |  |  |  |  |  |  |  |
| men |  |  |  |  |  |  |  |  |  |  |  |  |
| small-for-gestational-age |  | 0.86 | 3.09 | 0.78 |  | 0.85 |  | -0.91 | 2.85 | 0.75 |  | 0.37 |
| large-for-gestational-age |  | 7.33 | 3.23 | 0.02 |  | 0.01 |  | 5.30 | 2.96 | 0.07 |  | 0.03 |
| preterm birth |  | 1.35 | 4.49 | 0.76 |  | 0.96 |  | 0.93 | 4.21 | 0.83 |  | 0.96 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| women |  |  |  |  |  |  |  |  |  |  |  |  |
| small-for-gestational-age |  | 1.56 | 2.01 | 0.44 |  |  |  | 2.03 | 1.96 | 0.30 |  |  |
| large-for-gestational-age |  | -2.33 | 1.98 | 0.24 |  |  |  | -1.90 | 1.98 | 0.34 |  |  |
| preterm birth |  | 1.61 | 3.10 | 0.60 |  |  |  | 1.86 | 3.12 | 0.55 |  |  |
| † not log-transformed |  |  |  |  |  |  |  |  |  |  |  |  |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | model 3 |  |  |
|  |  | previous + BMI |  |  |
|  |  | beta | SE | p |  | p for interaction |
| gamma-glutamate transferase (GGT) |  |  |  |  |  |  |
| men |  |  |  |  |  |  |
| small-for-gestational-age |  | 0.02 | 0.05 | 0.68 |  | 0.14 |
| large-for-gestational-age |  | -0.05 | 0.05 | 0.29 |  | 0.81 |
| preterm birth |  | 0.12 | 0.07 | 0.07 |  | 0.01 |
|  |  |  |  |  |  |  |
| women |  |  |  |  |  |  |
| small-for-gestational-age |  | 0.09 | 0.03 | <0.01 |  |  |
| large-for-gestational-age |  | -0.05 | 0.03 | 0.05 |  |  |
| preterm birth |  | -0.06 | 0.04 | 0.11 |  |  |
|  |  |  |  |  |  |  |
| alanine transaminase (ALT) |  |  |  |  |  |  |
| men |  |  |  |  |  |  |
| small-for-gestational-age |  | 0.06 | 0.04 | 0.17 |  | 0.94 |
| large-for-gestational-age |  | -0.05 | 0.05 | 0.29 |  | 0.56 |
| preterm birth |  | 0.16 | 0.07 | 0.02 |  | <0.01 |
|  |  |  |  |  |  |  |
| women |  |  |  |  |  |  |
| small-for-gestational-age |  | 0.06 | 0.03 | 0.04 |  |  |
| large-for-gestational-age |  | 0.00 | 0.03 | 0.90 |  |  |
| preterm birth |  | -0.07 | 0.04 | 0.07 |  |  |
|  |  |  |  |  |  |  |
| aspartate transaminase (AST)  |  |  |  |  |  |  |
| men |  |  |  |  |  |  |
| small-for-gestational-age |  | 0.03 | 0.02 | 0.26 |  | † |
| large-for-gestational-age |  | -0.02 | 0.03 | 0.36 |  | 0.03 |
| preterm birth |  | 0.08 | 0.04 | 0.04 |  | 0.96 |
|  |  |  |  |  |  |  |
| women |  |  |  |  |  |  |
| small-for-gestational-age |  | 0.05 | 0.02 | <0.01 |  |  |
| large-for-gestational-age |  | 0.02 | 0.02 | 0.24 |  |  |
| preterm birth |  | 0.01 | 0.03 | 0.65 |  |  |
|  |  |  |  |  |  |  |
| fatty liver index (FLI) |  | BMI included in measurement |
| † Interaction model failed to converge |  |  |

|  |
| --- |
| Table 6. Birth outcomes as predictors of probable fatty liver on ultrasound, the Cardiovascular Risk in Young Finns Study (n= 2546)  |
|  |  | unadjusted |  | adjusted for age, sex, smoking, alcohol use, social class, physical activity |  | adjusted for previous + BMI |
|  |  | OR† | 95% CI |  | OR | 95% CI |  | OR | 95% CI |
| small-for-gestational-age |  | 1.82 | (1.32, 2.50) |  | 1.63 | (1.16, 2.29) |  | 1.75 | (1.21, 2.53) |
| large-for-gestational-age |  | 0.78 | (0.53, 1.14) |  | 0.78 | (0.52, 1.16) |  | 0.68 | (0.44, 1.05) |
| preterm birth |  | 2.46 | (1.59, 3.79) |  | 2.75 | (1.72, 4.39) |  | 2.84 | (1.70, 4.76) |
| low birthweight |  | 2.59 | (1.58, 4.25) |  | 2.41 | (1.42, 4.09) |  | 2.33 | (1.31, 4.16) |
| macrosomia |  | 0.82 | (0.60, 1.14) |  | 0.70 | (0.50, 0.99) |  | 0.60 | (0.41, 0.88) |
| † Reference category for all models is all participants not categorized as “case”.  |