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Thaware, P. K., McKenna, S., Patterson, C. C., Casey, C., & McCance, D. R. (2018). Maternal lipids at 28 weeks gestation and offspring adiposity at age 5-7 years. *The Journal of Clinical Endocrinology & Metabolism*, *103*(10), 3767–3772. https://doi.org/10.1210/jc.2018-00786

Published in:
The Journal of Clinical Endocrinology & Metabolism

Document Version:
Peer reviewed version

Maternal lipids at 28 weeks gestation and offspring adiposity at age 5-7 years

Parag K. Thaware[1,2], Sonia McKenna[3], Christopher C. Patterson[2], Claire Casey[2], David R. McCance [1,2,3]

1-Regional Centre for Endocrinology and Diabetes, Royal Victoria Hospital, Belfast, UK

2-Centre for Public Health, Queen's University Belfast, Belfast, U.K.

3-Royal Jubilee Maternity Hospital, Belfast, Northern Ireland, U.K.

Short title: Maternal lipids and offspring adiposity at 5-7 yrs

Keywords- Pregnancy, HAPO, lipid metabolism, anthropometry

Correspondence and reprint requests: Professor David R. McCance, Regional Centre for Endocrinology and Diabetes, Royal Victoria Hospital, 274 Grosvenor Road, Belfast, Northern Ireland, U.K. BT12 6BA. Phone: 0044 2890 633430, Fax: 0044 2890 310111;

E-mail: david.mccance@belfasttrust.hscni.net

Funding: The HAPO study was funded by grants from the National Institute of Child Health and Human Development and the National Institute of Diabetes and Digestive and Kidney Diseases (RO1-HD34242 and RO1- HD34243) and Diabetes UK (RD04/ 0002756), which supported the enrolment and collection of data on participants.

Abstract

Context- Obesity is a global epidemic, and there is a focus on identifying markers of obesity in children with a view to prevention.

Objective- We aimed to prospectively examine the association of maternal fasting lipids with adiposity in 5-7-year old offspring in a large observational study.

Design- 1612 pregnant women were recruited to the Belfast centre of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study in a large tertiary maternity hospital at an average of 28 weeks gestation. Maternal fasting total cholesterol, LDL-cholesterol (LDL-C), triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C) were estimated at 28 weeks gestation. At follow-up (5-7 years later), 1224 offspring were re-examined and adiposity expressed as body mass index (BMI) *Z* score (1990 British Growth Standard) and sum of skin fold thicknesses (triceps, subscapular and suprailiac). Statistical significance was more rigorously defined as $p<0.01$ to allow for multiple comparisons.

Results- No linear relation was found between maternal lipids and offspring BMI Z score or sum of skin folds ($p\geq0.01$) using correlation analysis. Using logistic regression, there was no relation between maternal lipids and offspring adiposity controlled for birthweight Z score, offspring age, offspring gender, smoking during pregnancy, maternal BMI during pregnancy and fasting glucose during pregnancy, ($p\geq0.01$), although the association between maternal LDL cholesterol and offspring BMI Z score $\geq85^{th}$ percentile approached significance [OR 1.15 (1.03 to 1.29) p=0.02].

Conclusion-Maternal 28 week gestational fasting lipids are not associated with offspring BMI or subcutaneous adiposity at age 5-7 years.

Précis: Maternal fasting lipids were measured during pregnancy and offspring adiposity was measured 5-7 years later. No culpable association between maternal lipids and offspring adiposity was observed.

Introduction

The concept of fuel mediated teratogenesis, as proposed by Freinkel in his 1980 Banting Lecture, postulated that altered fuel metabolism during pregnancy had a long lasting metabolic effect on the offspring(1). Although in the intervening years the focus has largely been on maternal glucose as the principal fetal fuel, Herrera and colleagues have observed that triglycerides are taken up by the placenta and hydrolysed to release free fatty acids in the foetus (2). Furthermore, the latter part of pregnancy is associated with a significant hyperlipidemia including hypercholesterolemia and hypertriglyceridemia.

The relationships of maternal lipids during pregnancy to birth outcomes have been documented. High maternal triglyceride (TG) and low maternal high density lipoprotein-cholesterol (HDL-C) have been associated with higher birth weight z-score, and subsequently macrosomia(3-5). Few studies however have examined this relation to longer term outcomes. Daraki and colleagues observed that an increase of one mmol/l in maternal cholesterol was associated with a greater offspring skinfold thickness at 4 years of age after adjustment for a number of confounders (6). In a large prospective study, an association was observed between maternal total cholesterol and offspring fat percentage at 5 years (7). Such an association, if present, would lend further support to the presence of developmental programming in the offspring based on fuel mediated teratogenesis.

The aim of this study was to examine the association between maternal lipids during pregnancy and later offspring adiposity at age 5-7 years controlled for relevant confounders including maternal body mass index (BMI), gestational glycaemia and offspring birth weight.

Materials and methods

Details of the methodology of the HAPO study have been published elsewhere (8-9)**.** Briefly, the HAPO study was a 15-centre multicultural and multinational study designed to examine the association between maternal hyperglycaemia, and adverse pregnancy outcomes with singleton pregnancies whose results on oral glucose tolerance test (OGTT) were below the thresholds for diabetes. All pregnant women at a given centre were eligible to participate. Each participant underwent a standard 75g OGTT between 24-32 weeks gestation (optimal-28 weeks), with sampling of plasma glucose fasting and at one hour and two hours. OGTT results were blinded to the clinician responsible for the care of the pregnant woman unless the fasting plasma glucose level exceeded 5.8 mmol/L or the 2-hour post-load level exceeded 11.1 mmol/L. A number of standardised questionnaires were used to determine information about the mother including age at OGTT, pre-pregnancy BMI, marital status, and years in education. All eligible women from the Belfast centre were invited to take part in a prospective observational study involving an additional fasting serum sample for lipids at 28 weeks gestation and long term follow up of their HAPO offspring. Offspring from these pregnancies had anthropometric measurements performed within 72 hours of birth.

Mothers were contacted 5-7 years after birth and invited to participate in a follow-up study for both the mother and the offspring. Similar questionnaires were used at follow-up to determine information about the mother. Examination of 5-7 year offspring included weight measured to the nearest 0.1 kg using Seca model 708 (Seca, Birmingham, UK.), and height measured to the nearest 0·1 cm using a regularly calibrated stadiometer. Skin fold thicknesses in the 5-7 year old offspring were measured at triceps, subscapular and suprailiac sites to the nearest 0·1 mm using Holtain skinfold calipers (Holtain, Crymych, U.K). Arithmetic means were derived from duplicate measurements for use in further statistical analysis.

Serum lipids (total cholesterol, TG and HDL-C) and plasma glucose levels were measured using a chemical analyzer (Roche C6000). Low-density lipoprotein cholesterol (LDL-C) was derived using the Friedewald equation if triglyceride levels did not exceed 4·52 mmol/L. The intra-assay CV's for cholesterol, HDL and triglycerides were on average 1.3%, 0.7% and 0.8%, respectively. The inter-assay CV's for cholesterol, HDL and triglycerides were on average 2.0%, 2.7% and 2.0%, respectively.

Based on BMI at the pregnancy OGTT, mothers were classified as obese (BMI≥33 kg/m^2), overweight (BMI 28·5-32·9 kg/m^2) or normal weight (BMI<28·5 kg/m^2) as per previously reported cut offs for BMI categories in late pregnancy(10). Offspring birth weight and BMI at 5-7 years were converted to a standard deviation (Z) score using the age and gender- specific 1990 British Growth Standard(11). A summary skin fold thickness measure was derived as the sum of skin folds (SSF) from each of the measured sites at 5-7 years age. Adiposity at birth was evaluated by birth weight *Z* score and using birth weight *Z* score ≥ 90th percentile to define large for gestational age. At 5-7 years the measures of offspring adiposity included BMI Z score, BMI Z score ≥85th (overweight or obese) and ≥95th (obese) percentile, offspring SSF and SSF ≥ 90th percentile.

Statistical analysis

Statistical analyses were performed using SPSS 24. Baseline characteristics are presented as mean (±SD) or proportions and categorized by offspring at 6 year BMI z-score with independent samples t-test or chi-square test. For analysis using continuous variables, the distribution of sum of skin folds and maternal TG showed positive skew and these were logarithmically transformed and summarised as the geometric means and interquartile range. Correlation analysis was used to examine the crude relationship between variables. The association between maternal lipids and offspring categorical outcomes were examined using

logistic regression, with and without adjustment for the selected variables. The logistic regression used a number of models; model 1: birth weight z-score, offspring age, offspring gender and smoking during pregnancy; model 2: model one plus maternal BMI at OGTT and model 3: model 2 and maternal fasting plasma glucose at 28 weeks gestation. To allow for the multitude of statistical analyses, a stricter significance level of $p< 0.01$ was adopted for all linear and logistic regression analyses, while the conventional level of $p<0·05$ was used for comparison of baseline participant characteristics.

Ethical approval was obtained from the Northern Ireland Regional Ethics Committee and the research adhered to the tenets of the Declaration of Helsinki.

Results

Recruitment and follow-up numbers from the Belfast HAPO centre are presented in **Supplemental Figure 1**. The number of participants was slightly reduced in some analyses due to unavailability of LDL-C in 21 mothers and Sum of the skin folds in six children. The minimum number of mother-child pairs included in analysis involving both these measures was 1197 (75% of live births).

Participant characteristics are shown in **Supplemental Table 1**. Of the 1612 White European women who had remained blinded during the HAPO study, 388 were not included in the study as elaborated in supplemental figure 1. Compared with non-participants, participating women were older (mean ± SD: 30·0 ± 5.4 vs 28·6 ± 5.6 years, p <0·001), leaner at OGTT (mean BMI 28·1 ± 4.3 vs 28·8 ± 5.4 kg/m^2, p 0·04), less likely to be obese (12·3% vs 18·1%, p 0·01), more educated (15·0 ± 2.9 vs 14·4 ± 2.7 years, p ≤0·001), and less likely to have smoked in pregnancy (21·6% vs 32·0%, p <0·001). Gestational LDL-C was higher in participating mothers (3·9 ± 1.2 vs 3·7 ± 1.2 mmol/L, p=0·02). There were no significant differences between participant and non-participants in offspring adiposity measures at birth.

Table 1 shows the maternal and offspring characteristics by offspring BMI Z score (< 0.00 vs > 0.00) at 5-7 years. As expected, maternal BMI at 28 weeks gestation was significantly different across the two subgroups (27.1 ± 3.8 vs 28.7 ± 4.6, p≤0.001). Women were more likely to be obese during pregnancy whose offspring had a BMI z-score >0.00 at 5-7 years compared to ≤ 0.00 (76.8% vs 23.2%)(≤0.001). No significant differences were observed in maternal lipid biomarkers between the two offspring BMI z-score groups. In terms of offspring characteristics, birthweight z-score (-0.3 ± 0.9 vs 0.0 ± 0.9 p ≤0.001) and sum of skinfolds thickness [1.1 (1.1-1.3 vs 1.1 (1.0-1.2) p=0.002] were significantly different

158 between the two subgroups of BMI z-scores. These associations were also observed in the
159 offspring at the 5-7 year follow-up.

160 There was no discernible relationship between maternal serum lipids during pregnancy (total
161 cholesterol, TG, LDL-C, HDL-C) and offspring BMI Z score at 5-7 year follow up on scatter
162 plots and correlation analysis (**Figure 1**). A similar lack of association was observed between
163 maternal lipids and offspring sum of skin folds at 5-7 years age both on scatter plots (**Figure**
164 **2**).

165 **Table 2** shows the association of three measures of excess offspring adiposity at follow up
166 with each of the maternal lipid measures using unadjusted and adjusted logistic regression
167 analysis. In unadjusted analyses, there was no association between maternal LDL-C levels
168 and offspring BMI *Z* score ≥85th percentile (p=0.062). After adjustment for offspring birth
169 weight standard deviation score, age at follow up, gender and smoking during pregnancy this
170 relation grew stronger, but remained non-significant at the p<0·01 level (p=0.051). When
171 BMI at OGTT was added to the analysis, the relation grew even stronger (p=0.016), and
172 remained unchanged when maternal fasting glucose was added to the analysis. Maternal TG
173 during pregnancy showed an association with follow up offspring BMI *Z* score ≥85th
174 percentile and sum of skin folds ≥90th percentile, although neither result was significant at the
175 p<0·01 level in unadjusted analyses. Following adjustment, both these relations remained
176 non-significant. The above lipid analyses were repeated and stratified according to BMI at
177 OGTT categories, and regression analyses were repeated as per table 2 with the same
178 confounding variables, with the exception of the removal of BMI at OGTT due to
179 stratification by the same variable. No significant associations were observed between the
180 various weight categories with maternal lipids and offspring adiposity outcomes (data not
181 shown).

182

Discussion

In this carefully characterised cohort and after controlling for relevant confounding variables, we found no association between any of the measured maternal lipids during pregnancy and later offspring adiposity, although the relation between maternal LDL-cholesterol and offspring BMI SDS ≥ 85th percentile approached significance.

Obesity is generally thought to be the result of a combination of nature and nurture but a specific intra uterine influence has increasingly been recognised (12-13). In this regard, the relationship between maternal gestational lipids and later offspring obesity is of considerable interest. There is a physiological rise in maternal lipids during pregnancy that starts around mid second trimester reaching its peak in the third trimester(12). One putative mechanism may relate to the delivery of energy excess to the offspring from the energy rich triglycerides that have previously been related to excess offspring birth weight(13). However, we are unable to support this finding as we found no relation between fasting maternal triglyceride and offspring obesity risk at 5-7 years age. We also found a similar lack of association between hyperglycemia during pregnancy, the principal materno-fetal fuel, and later offspring obesity, as previously reported using data from the same cohort(14). There was a tendency for offspring BMI Z score to be ≥85th percentile with higher maternal LDL cholesterol. While this did not meet our predefined 1% level of significance, the association was significant at the conventional 5% significance level. This was after adjustment for important potential confounders including maternal BMI, gestational glycaemia and offspring birth weight. The observation needs to be replicated.

We are aware of few previous human studies which have directly examined these relationships. One study examined patients with familial hypercholesterolemia inherited either maternally or paternally and reported primarily on lipid differences between the two

groups in adult offspring (18-85 years)(15). Like us, they found no difference in mean BMI between the groups even though offspring with maternal inheritance would be expected to experience a significantly greater hypercholesterolemic intrauterine milieu. Daraki and colleagues examined early pregnancy measures of maternal lipids and the associations with offspring adiposity measures in 348 offspring aged 4 years. They observed an increase of 1.00 mmol/L in fasting serum cholesterol levels was associated with a 3.30 (95% CI 1.41, 5.20) mm greater skinfold thickness at 4 years of age in adjusted analysis (6).A community-based study of Amsterdam Born ChilDren (ABCD) demonstrated an independent association between non fasting maternal free fatty acids during early pregnancy and offspring adiposity aged 5-6 years, however maternal triglycerides were only significantly related to waist height ratio independent of confounders while the association with offspring body fat percentage and BMI became non-significant after adjustment for confounders (7). It is unclear why the results of these latter two studies differ from those of the present study although of note is the fact that subject numbers in the first study were relatively small and in both studies measurement of maternal lipids was in early gestation. In addition, the authors of the ABCD study concluded that maternal BMI (a recalled rather than directly measured variable) was the dominant influence on child obesity and they were unable to explain the disparity in offspring adiposity associations between maternal free fatty acids (FFA) and triglyceride measurements (7).

Our long term prospective study has several strengths including a high follow up rate, a large homogenous cohort and adjustment for multiple potentially confounding factors. The double blinding of mothers during pregnancy is also unique and allows assessment of the relationships without impact from glucose lowering interventions during pregnancy

There are some limitations to our data. Firstly, unlike placental glucose transfer, transfer of both maternal cholesterol and triglycerides is more complex and regulated by enzymatic

232 systems. It is currently unclear whether such processes display heterogeneity in materno-fetal
233 lipid transfer independent of maternal lipids. While further evidence is awaited, we have
234 interpreted our results on the assumption that maternal hyperlipidaemia will reflect
235 proportionally on the fetal milieu. Also, the present study is confined to women of White
236 European origin and therefore the data need to be extrapolated with caution to other
237 population groups, and to other offspring ages. There also may be an additional rise in
238 maternal lipids after 28 weeks gestation, which may have a larger impact on offspring
239 obesity.

240 In summary, this study shows that maternal third trimester lipids are not associated with an
241 increased risk for offspring obesity by age 5-7 years. Whether such a relation exists in older
242 offspring is unknown but a similar long term follow up study is currently in progress among
243 8-12 year old HAPO offspring in the Belfast centre.

244

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289 Table 1: Characteristics of participant mothers and offspring by offspring BMI z-score at 5-7
290 years age follow-up

	Offspring BMI Z-score at 6 yr ≤ 0.00 (n=450)	Offspring BMI Z-score at 6 yr >0.00 (n=867)	p-value
Maternal			
Age at pregnancy OGTT (yr)	30.2 ± 5.3	29.9 ± 5.4	0.36
BMI at pregnancy OGTT (kg/m^2)	27.1 ± 3.8	28.7 ± 4.6	≤0.001
BMI category at pregnancy OGTT			
<28·5 kg/m^2	328 (40.6%)	480 (59.4%)	
28·5-32·9 kg/m^2	84 (24.4%)	260 (75.6%)	
≥33 kg/m^2	38 (23.2%)	126 (76.8%)	≤0.001
Education (yrs)	15.1 ± 2.8	15.1 ± 2.9	0.98
Fasting 28th week lipids (mmol/L)			
Total cholesterol	6.5 ± 1.4	6.5 ± 1.5	0.60
Triglycerides*	2.1 (1.7-2.6)	2.1 (1.7-2.6)	0.74
LDL cholesterol	3.9 ± 1.1	3.8 ± 1.2	0.74
HDL cholesterol	1.7 ± 0.4	1.7 ± 0.4	0.35
Fasting glucose at 28th week OGTT (mmol/L)	4.6 ± 0.3	4.6 ± 0.3	0.02
1-hour glucose at 28th week OGTT (mmol/L)	7.4 ± 1.6	7.5 ± 1.6	0.14
2-hour glucose at 28th week OGTT (mmol/L)	6.0 ± 1.1	6.1 ± 1.2	0.14
Smoked cigarettes during pregnancy	89 (19.8%)	191 (22.0%)	0.34
Drank alcohol during pregnancy	120 (26.7%)	239 (27.6%)	0.73
Married or co-habiting during pregnancy	390 (86.7%)	734 (84.6%)	0.33
Offspring			
Female gender	222 (49.3%)	416 (48.0%)	0.64
Birth weight Z score	-0.3 ± 0.9	0.0 ± 0.9	≤0.001
Macrosomic	42 (9.3%)	109 (12.6%)	0.08
Neonatal SSF*	1.1 (1.1-1.3)	1.1 (1.0-1.2)	0.002
Age at follow up (yr)	6.3 ± 0.5	6.4 ± 0.5	0.86
BMI at follow up (kg/m^2)	14.8 ± 0.6	17.3 ± 1.8	≤0.001
BMI Z Score at follow up	-0.6 ± 0.5	1.0 ±0.8	≤0.001
BMI Z Score category			
≥85th percentile	0 (0%)	318 (36.7%)	≤0.001

≥95th percentile	0 (0%)	143 (16.5%)	≤0.001
SSF at follow up (mm)*	1.3 (1.2-1.3)	1.4 (1.3-1.5)	≤0.001
SSF ≥90th percentile	1 (0.2%)	129 (15%)	≤0.001

Data represent mean (standard deviation) or count (percentage) or geometric mean (interquartile range) for skewed variables;

p-value is determined by independent t-test for continuous variables and chi-square analysis for categorical variables.

*Heavily positively skewed variable

BMI, body mass index; OGTT, oral glucose tolerance test; SSF, sum of skinfold

Table 2: Logistic regression models showing maternal lipids during pregnancy at 28 weeks gestation in relation to excess adiposity outcomes in the offspring at age 5-7 years

	Total cholesterol	Triglyceride†	LDL-cholesterol	HDL-cholesterol
Offspring BMI *Z* score≥85th percentile (n 1224‡)				
Unadjusted	1.07 (0.97 to 1.17)	1.30 (1.01 to 1.68)*	1.11 (1.00 to 1.24)	0.83 (0.62 to 1.12)
Model 1	1.08 (0.98 to 1.18)	1.22 (0.94 to 1.57)	1.12 (1.00 to 1.25)*	0.91 (0.67 to 1.24)
Model 2	1.10 (1.00 to 1.21)	1.04 (0.80 to 1.36)	1.15 (1.03 to 1.29)*	1.03 (0.75 to 1.42)
Model 3	1.10 (1.00 to 1.21)	1.04 (0.80 to 1.35)	1.15 (1.03 to 1.29)*	1.03 (0.75 to 1.43)
Offspring BMI *Z* score≥95th percentile (n 1224‡)				
Unadjusted	1.00 (0.88 to 1.13)	1.27 (0.90 to 1.79)	1.03 (0.89 to 1.19)	0.72 (0.48 to 1.07)
Model 1	1.02 (0.90 to 1.15)	1.17 (0.83 to 1.65)	1.06 (0.92 to 1.24)	0.69 (0.45 to 1.05)
Model 2	1.04 (0.92 to 1.19)	0.95 (0.67 to 1.36)	1.11 (0.95 to 1.30)	0.80 (0.51 to 1.24)
Model 3	1.05 (0.92 to 1.19)	0.94 (0.66 to 1.34)	1.11 (0.95 to 1.30)	0.81 (0.52 to 1.26)
Offspring sum of skin folds (mm)≥90th percentile (n 1218§)				
Unadjusted	1.00 (0.88 to 1.14)	1.45 (1.01 to 2.09)*	1.00 (0.86 to 1.17)	0.85 (0.56 to 1.30)
Model 1	1.02 (0.89 to 1.17)	1.33 (0.91 to 1.95)	1.04 (0.88 to 1.23)	0.81 (0.51 to 1.27)
Model 2	1.04 (0.90 to 1.20)	1.11 (0.76 to 1.63)	1.08 (0.91 to 1.28)	0.90 (0.56 to 1.44)
Model 3	1.04 (0.90 to 1.20)	1.10 (0.75 to 1.61)	1.08 (0.91 to 1.28)	0.91 (0.57 to 1.45)

Model 1- Adjusted for offspring birth weight standard deviation score, age at follow up, gender and smoking during pregnancy.

Model 2- Adjusted for model 1 plus maternal BMI at OGTT

Model 3- Adjusted for model 2 plus maternal fasting plasma glucose

* Statistically significant at $p \leq 0.05$

†- Data represent odd ratio (95% confidence interval) with p value per doubling in maternal triglyceride

‡n=1203 and §n=1197 for models including LDL Cholesterol

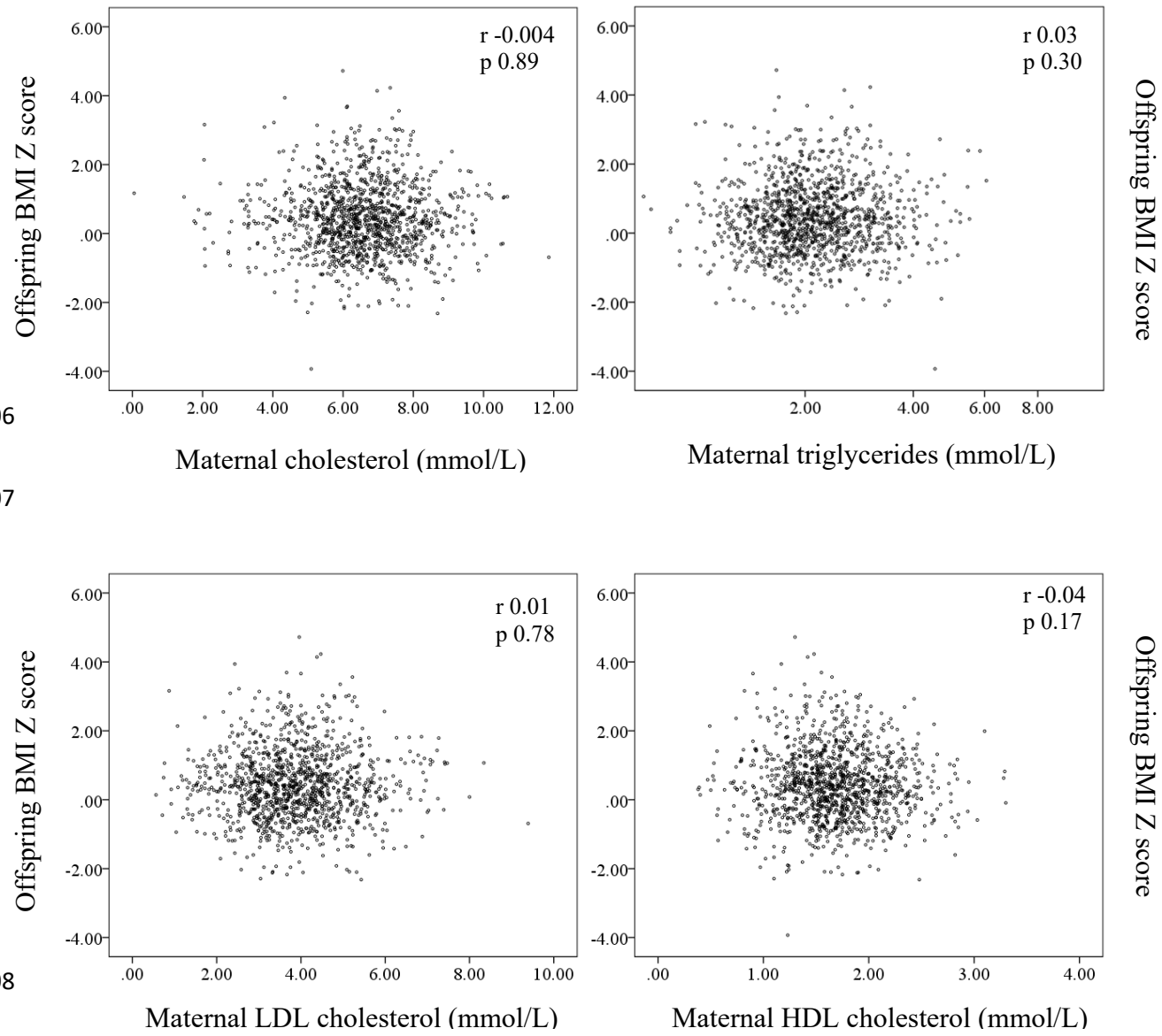

Figure 1: Scatter plots comparing maternal lipids during pregnancy on X-axes and offspring BMI Z score on Y axes in 5-7 year old offspring.

Plots show relation between maternal fasting lipid parameters in mmol/L at an average of 28 week gestation on X axes and offspring BMI Z score on the Y axes with Pearson's correlation coefficients and p value.

BMI, body mass index LDL, low-density lipoprotein HDL, high-density lipoprotein

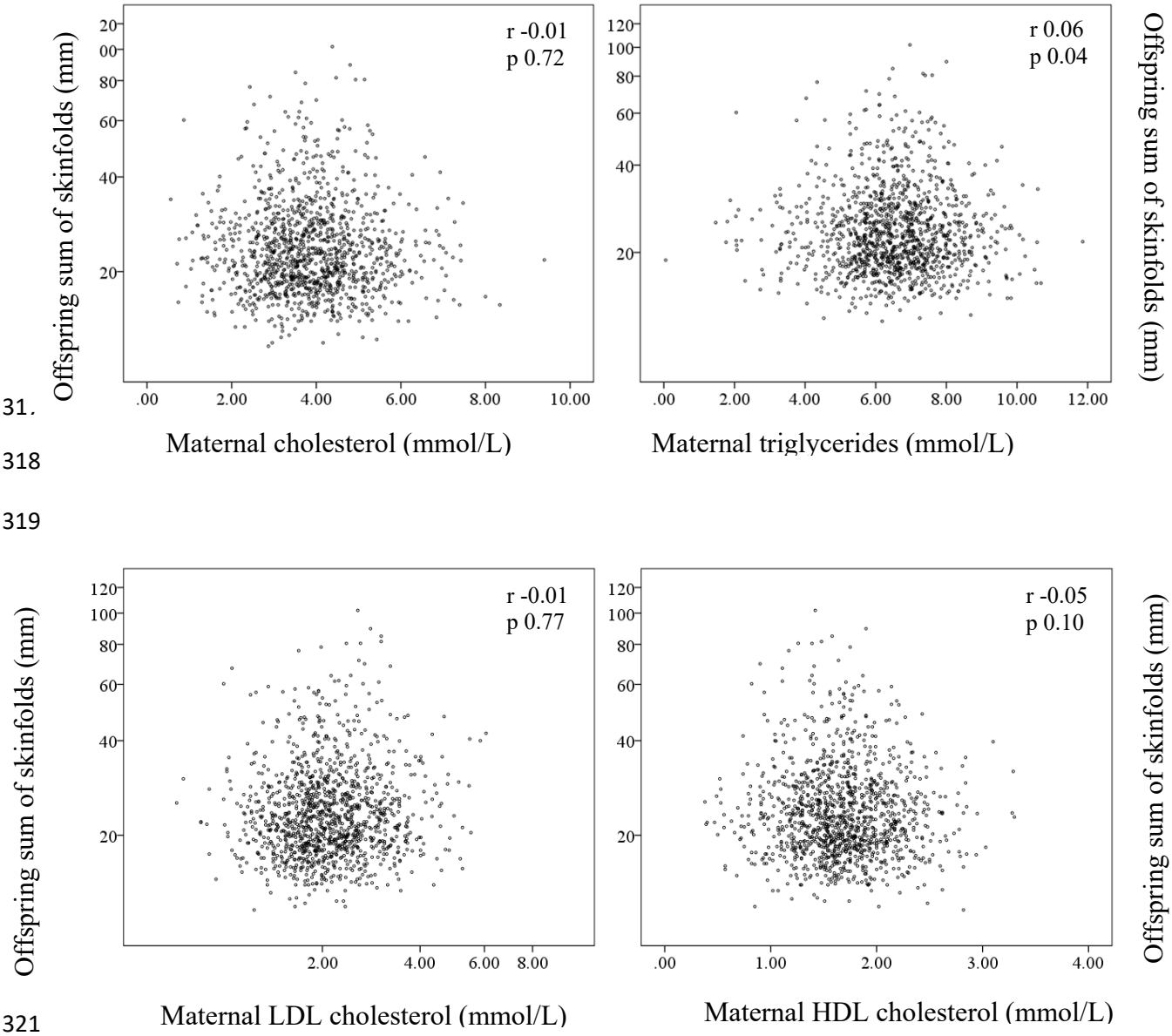

Figure 2: Scatter plots comparing maternal lipids during pregnancy on X-axes and 5 offspring sum of skinfolds on Y axes in 5-7 year old offspring

Plots show relation between maternal fasting lipid parameters in mmol/L at an average of 28 weeks gestation on X axes and offspring sum of skin folds on the Y axes with Pearson's correlation coefficients and p value.

LDL, low-density lipoprotein HDL, high-density lipoprotein