

This is a self-archived version of an original article. This version may differ from the original in pagination and typographic details.

Author(s): Westberg, Anna P.; Kautiainen, Hannu; Salonen, Minna K.; Kajantie, Eero; von Bonsdorff, Mikaela; Eriksson, Johan G.

Title: The impact of maternal weight in pregnancy on glucose metabolism in non-diabetic offspring in late adulthood

Year: 2019

Version: Accepted version (Final draft)

Copyright: © 2019 Elsevier B.V.

Rights: CC BY-NC-ND 4.0

Rights url: <https://creativecommons.org/licenses/by-nc-nd/4.0/>

Please cite the original version:

Westberg, A. P., Kautiainen, H., Salonen, M. K., Kajantie, E., von Bonsdorff, M., & Eriksson, J. G. (2019). The impact of maternal weight in pregnancy on glucose metabolism in non-diabetic offspring in late adulthood. *Diabetes Research and Clinical Practice*, 158, Article 107926. <https://doi.org/10.1016/j.diabres.2019.107926>

Journal Pre-proofs

The impact of maternal weight in pregnancy on glucose metabolism in non-diabetic offspring in late adulthood

Anna P. Westberg, Hannu Kautiainen, Minna K. Salonen, Eero Kajantie, Mikaela von Bonsdorff, Johan G. Eriksson

PII: S0168-8227(19)31395-6
DOI: <https://doi.org/10.1016/j.diabres.2019.107926>
Reference: DIAB 107926

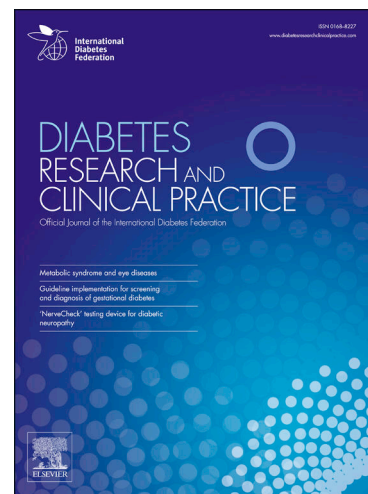
To appear in: *Diabetes Research and Clinical Practice*

Received Date: 30 September 2019
Revised Date: 4 November 2019
Accepted Date: 11 November 2019

Please cite this article as: A.P. Westberg, H. Kautiainen, M.K. Salonen, E. Kajantie, M. von Bonsdorff, J.G. Eriksson, The impact of maternal weight in pregnancy on glucose metabolism in non-diabetic offspring in late adulthood, *Diabetes Research and Clinical Practice* (2019), doi: <https://doi.org/10.1016/j.diabres.2019.107926>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2019 Published by Elsevier B.V.



The impact of maternal weight in pregnancy on glucose metabolism in non-diabetic offspring in late adulthood

Anna P. Westberg^{1,2}, Hannu Kautiainen^{1,3}, Minna K. Salonen^{1,4}, Eero Kajantie^{4,5,6}, Mikaela von Bonsdorff^{1,7}, Johan G. Eriksson^{1,2,4,8,9}

1. Folkhälsan Research Center, Helsinki, Finland.
2. Department of General Practice and Primary Health Care, University of Helsinki and Helsinki University Hospital, Helsinki, Finland.
3. Primary Health Care Unit, Kuopio University Hospital, Kuopio, Finland.
4. Department of Public Health Solutions, Unit of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki
5. Children's Hospital, Helsinki University Hospital and University of Helsinki, Helsinki, Finland.
6. PEDEGO Research Unit, MRC Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland.
7. Gerontology Research Center and Faculty of Sport and Health Sciences, University of Jyväskylä, Finland
8. National University of Singapore, Yong Loo Lin School of Medicine, Department of Obstetrics and Gynecology, Singapore
9. Singapore Institute for Clinical Sciences, Agency for Science, Technology, and Research, Singapore;

Correspondence: Anna P. Westberg
Department of General Practice and Primary Health Care, University of Helsinki
PO Box 20
00014 University of Helsinki, Helsinki, Finland
Tel: +358 294 1911, e-mail: anna.westberg@helsinki.fi
Orcid ID: 0000-0001-7585-3647

Abstract

Aims

We aimed to examine the association between maternal adiposity and glucose metabolism in adult offspring without diabetes, simultaneous taking offspring own adiposity into account.

Methods

This longitudinal birth cohort study (Helsinki Birth Cohort Study) included 1,440 non-diabetic subjects examined at a mean age of 62 years. Subjects were divided into quartiles according to maternal body mass index (BMI). The impact of maternal BMI on offspring body composition was also studied.

Results

There were no differences in fasting glucose between the groups. In men, maternal BMI was inversely associated with mean 2-hour glucose concentration after a 75 g oral glucose tolerance test ($p < 0.001$) and mean homeostatic model assessment of insulin resistance (HOMA-IR) ($p = 0.049$).

According to the subjects' own BMI, high maternal BMI was associated with lower 2-hour glucose concentrations only in non-obese men and with lower HOMA-IR only in obese men. Maternal BMI was not associated with glucose concentrations nor with HOMA-IR in women. In addition, maternal BMI was positively associated with a higher offspring lean body mass in men.

Conclusions

High maternal BMI was associated with lower 2-hour plasma glucose concentration, especially in non-obese men. Offspring lean body mass may be a mediating factor for the association.

Keywords: Maternal obesity, offspring health, BMI, glucose metabolism, insulin sensitivity

Introduction

The obesity epidemic is a major challenge to global health today also involving women of reproductive age^{1,2}. Maternal pre-pregnancy obesity and excess gestational weight gain during pregnancy are well-recognized risk factors for immediate adverse pregnancy outcomes, such as gestational diabetes and pre-eclampsia³⁻⁵. Furthermore, multiple studies have recently focused on the impact of maternal adiposity on offspring health later in life⁶.

The mechanisms underlying the association between maternal obesity and offspring later health are likely to be multifactorial and to include epigenetic programming in early life⁷. In animal studies, maternal adiposity has been found to alter the metabolic regulatory pathways of the fetus, including shifting the hypothalamic response to leptin, changing appetite control and altering beta cell function in the pancreas^{8,9}. Additionally, studies in human subjects show that maternal obesity is linked to changes in DNA methylation in sites associated with offspring adiposity, indicating epigenetic remodeling¹⁰.

In regard of cardiometabolic outcomes, maternal obesity has been linked to childhood adiposity, adverse body-fat distribution, adverse lipid profile, elevated blood pressure and insulin resistance in the offspring¹¹⁻¹³. Childhood body mass index (BMI) might be a mediating factor between maternal BMI and the other cardiometabolic outcomes^{11,14}. Similar results have been reported in adolescents and young adults¹⁵⁻¹⁸.

The associations between maternal BMI and offspring cardiometabolic outcomes in late adulthood have been less studied. A birth cohort study in the UK showed an association between maternal obesity and all-cause mortality and cardiovascular events in adult offspring¹⁹. In previous studies from the Helsinki Birth Cohort Study (HBCS), we found that maternal adiposity increased the risk of cardiovascular disease and type 2 diabetes in the offspring. The association for type 2 diabetes was stronger in women.²⁰

In this study, we focused on the impact of maternal BMI on glucose and insulin metabolism in non-diabetic offspring in late adulthood. Impaired fasting glucose, impaired glucose tolerance and insulin resistance are known risk factors for type 2 diabetes²¹. Based on previous studies, we hypothesized that a high maternal BMI would be linked to impaired glucose regulation and insulin resistance in the offspring.

Methods

This study is a part of the HBCS, a cohort consisting of 13,345 subjects who were born in one of the two largest delivery hospitals in Helsinki in 1934-1944 and who lived in Finland in 1971, when all Finnish residents received a unique social security number. In 2001-2004, 2,003 cohort members participated in a clinical examination. This clinical cohort was obtained by sending a questionnaire to all subjects from HBCS born at Helsinki University Hospital and living in Finland in year 2000 (n= 8,760). Out of the 6, 874 individuals who responded, 2,901 were randomly chosen to participate and, 2,003 of them did.

In this particular study, subjects with previously and newly diagnosed diabetes were excluded (n=315). These subjects were identified from the nationwide prescription register of the Social Insurance Institution (SII) as receiving special reimbursement for diabetes medication costs (information available from year 1964) and/or having purchased drugs for treatment of diabetes (available from year 1995). In Finland, diabetes medication is partly compensated by the state, and in order to receive the reimbursement, one must be diagnosed by a physician and approved by a physician at the SII. Newly diagnosed diabetes was based upon findings in the oral glucose tolerance test (OGTT) performed in association with the clinical study. Additionally, 244 subjects were excluded because they had incomplete data on maternal weight and height and 4 subjects were excluded because they lacked information about diabetes. Finally, this study cohort included 1,440 non-diabetic subjects who attended the clinical examination, had complete data on maternal weight and height as well as the main outcome variables in this study.

Information on the subjects and their mothers was collected from hospital birth records, child welfare records and school healthcare records. Data include information on maternal weight in late pregnancy, maternal height, maternal age at delivery, parity, gestational age and birth weight and height. Maternal BMI was calculated as late pregnancy weight/height² and maternal body surface area (BSA) was calculated by using the Mosteller formula²². We also calculated the subjects' ponderal index at birth with the formula birth weight/birth height³.

Glucose tolerance was assessed with a two-hour 75 g OGTT, and glucose concentrations were measured at baseline (FPG) and at two hours (2hPG) and expressed as mmol/L. Plasma insulin concentrations were measured at fasting and at two hours. HOMA-IR was used as a proxy for insulin sensitivity and HOMA-IR was calculated with the formula (fasting plasma glucose (mmol/l) x fasting serum insulin (mU/l))/22.5. The main outcomes were 2hPG and HOMA-IR.

Measurements acquired at the clinical examination included subjects' adult weight and height, waist circumference, lean body mass, fat percent, blood pressure, cholesterol and triglycerides concentrations and high sensitive C-reactive protein (hs-CRP). Subjects' own BMI was calculated as adult weight/height² and BSA by using the Mosteller formula. Blood pressure was measured from the right arm in a sitting position and the mean of two successive readings was used. Blood was drawn for the measurement of glucose, insulin, lipids and inflammatory markers. Lean body mass and body fat percentage were assessed by using an eight-polar tactile electrode system (Bio-impedance, InBody 3.0). The methods used to measure glucose and insulin concentrations, blood pressure, cholesterol concentrations, triglyceride concentrations and hs-CRP are described in detail in Eriksson et al.²³. Subjects' smoking status was assessed with a questionnaire and defined as whether currently smoking. The amount of leisure-time physical activity (LTPA) was based on a 12-month validated exercise questionnaire; the Kuopio Ischemic heart disease Risk Factor Study and physical activity was presented as metabolic equivalent of task (MET) per week²⁴. The study was approved by the Ethics Committee of Hospital District of Helsinki and Uusimaa and conducted according to guidelines in the Declaration of Helsinki. All subjects gave a written informed consent.

Statistical analyses

The maternal and offspring characteristics are presented as means with standard deviation (SD) for continuous variables and as frequencies with percentages for categorical variables. For describing the characteristics of the men and women they were divided into quartiles according to maternal BMI. The quartiles were maternal BMI <24.6 kg/m² (quartile I), 24.6-26.2 kg/m² (quartile II), 26.3-28.0 kg/m² (quartile III) and >28.0 kg/m² (quartile IV). In further analyses the men and women were divided into three groups according to their own adult BMI. The BMI cutoffs for overweight and obesity were used, with BMI <25.0 kg/m² in the lowest BMI group, 25.0-29.9 kg/m² in the middle BMI group and ≥30 kg/m² in the highest BMI group²⁵. Statistical significances for the unadjusted hypothesis of linearity across categories of maternal BMI were evaluated by using the Cochran-Armitage test for trend and analysis of variance with an appropriate contrast. Adjusted hypothesis of linearity (orthogonal polynomial) was evaluated using analysis of covariance. Models were adjusted for age, BMI, smoking and LTPA as covariates. The bootstrap method was used when the theoretical distribution of the test statistics was unknown or in the case of violation of the assumptions (e.g. non-normality). The normality of variables was evaluated using the Shapiro-Wilk W test. Stata 15.0 (StataCorp LP; College Station, Texas, USA) statistical package was used for the analysis.

Results

Table 1 shows maternal and neonatal characteristics according to quartiles of maternal BMI. Women in the highest maternal BMI quartile were older at the time of delivery, had a bigger BSA

and a higher parity. Gestational age, birth weight, birth length and ponderal index increased across the maternal BMI quartiles.

Table 2 shows adult characteristics according to maternal BMI quartiles for men and women. Both among men and women, the subjects' own BSA, adult weight, BMI and lean body mass increased across the maternal BMI quartiles. Women had a bigger waist circumference and a higher body fat percentage in the higher maternal BMI groups.

In men, no difference was observed in FPG according to maternal BMI (results not shown). In men 2-hour glucose concentration was 6.56 mmol/l in the highest maternal BMI group and 7.24 mmol/l in the lowest group (p for trend across maternal BMI quartiles <0.001 , adjusted for age, BMI, smoking and LTPA). HOMA-IR was 2.78 in the lowest maternal BMI quartile, 2.61 in maternal BMI quartiles II and III and 2.66 in the highest maternal BMI quartile (p for trend 0.049 across maternal BMI quartiles adjusted for age, BMI, smoking and LTPA). There were no significant differences in women in fasting or 2-hour glucose concentrations nor in HOMA-IR according to maternal BMI.

Figure 1 shows fasting and 2-hour plasma glucose concentrations according to quartiles of maternal BMI for men and women across adult BMI groups. In men with BMI <25.0 kg/m², there was a significant decrease in 2-hour glucose concentrations across maternal BMI groups (p for trend =0.002 after adjustment for age, BMI, smoking and LTPA). Similar results were observed in men with BMI between 25.0 and 29.9 kg/m² (adjusted p for trend=0.023). No such trend was observed in FPG and maternal BMI in men. There were no significant associations between maternal BMI and glucose concentrations in women in different adult BMI groups.

Figure 2 shows the trend of HOMA-IR according to quartiles of maternal BMI for men and women across adult BMI groups. In men with BMI ≥ 30 kg/m², there was a decrease in HOMA-IR across maternal BMI groups (p for trend =0.049, adjusted for age, BMI, smoking and LTPA). There was no significant difference in HOMA-IR according to maternal BMI in non-obese men nor in women. In men, lean body mass increased across maternal BMI (p for trend 0.043 adjusted for age, BMI, smoking and LTPA, results not shown). In women the corresponding p -value was 0.18 (adjusted for age, BMI, smoking and LTPA, results not shown).

Discussion

Within a cohort of 1,440 non-diabetic subjects from the HBCS, we investigated the impact of maternal adiposity on adult offspring glucose concentrations and insulin sensitivity, according to subjects own BMI. A high maternal BMI was related with a better glucose metabolism, especially in non-obese men. Furthermore, maternal BMI was linked to a better insulin sensitivity in obese men. In women, there was no association between maternal BMI and glucose-insulin metabolism. The strengths of this study include a long follow up period and reliable information about the mothers and the subjects at birth from hospital birth records. In this study, the subjects were followed up from birth until the mean age of 62 years. The subjects' adulthood characteristic, such as weight and height, were reliably measured at clinical examinations. Plasma glucose and insulin concentrations were retrieved from a blood test taken at the clinical examination and HOMA-IR is considered to be an appropriate tool for measuring insulin sensitivity in epidemiological studies²⁶. We also had the possibility to adjust for variables that are often lacking in epidemiological studies, such as smoking status and physical activity.

A limitation to this study is that the analyses are based on maternal BMI prior to delivery, since we do not have information about pre-pregnancy BMI. Neither were we able to adjust for gestational diabetes, since it was not diagnosed in pregnant women in Finland in 1930s and 1940s. Gestational diabetes has been linked to unfavorable effects on maternal and cord blood metabolomes that may mediate programming of obesity and cardiovascular events²⁷. However, maternal obesity is independently associated with adverse offspring neonatal outcomes also in mothers with gestational diabetes²⁸. As with most observational studies regarding developmental origins of diseases, we are

unable to differentiate the underlying impact of genetic, environmental and epigenetic factors or to confirm causality. Further, we do not have information about paternal characteristics', since information about the fathers was not available from hospital records. We are thus unable to elucidate the influences of paternal genetic and epigenetic traits. Hypothetically, paternal weight could alter the results in a way that we are not able to detect due to lack of data.

This study includes subjects who were alive and healthy enough to attend a clinical examination at mean age of 62 years and who did not suffer from diabetes at the time. We excluded subjects with diabetes, so that diabetes and diabetes medication would not interfere with the glucose and insulin measurements. On the other hand, the requirement of offspring survival until adult age and the exclusion of subjects with diabetes may cause a selection bias.

Previous studies have shown associations between maternal adiposity and offspring obesity and cardiovascular risk factors in children, adolescents and young adults¹¹⁻¹⁸. However, only a few studies have focused on the risk of diabetes and cardiovascular disease in offspring in late adulthood according to maternal adiposity^{19,20,23}. In HBCS, we have previously shown an association between maternal BMI and type 2 diabetes in adult offspring, particularly in women, but not between maternal BMI and offspring fasting glucose concentration or HOMA-IR^{20,23}. The present study adds to previous studies by focusing solely on non-diabetic offspring and by simultaneously taking offspring own adult BMI into account. In addition, we included 2-hour glucose concentration as a main outcome.

Differences in adult body composition might partly explain the results. Preceding studies from HBCS have shown that low birth weight predicted lower lean body mass in adulthood and that a high birth weight in combination with a high maternal BMI was associated with an adverse body composition in adulthood^{23,29}. In this study, men and women with higher maternal BMI had a higher lean body mass in the crude model. After adjustment for age, BMI, smoking and LTPA, there was a significant positive relationship between maternal BMI and lean body mass, but only in men. There is some evidence suggesting that a low muscle mass is a risk factor for type 2 diabetes and that it is also associated with poorer glucose metabolism and insulin sensitivity in subjects without diabetes^{30,31}. Skeletal muscle is a major organ of glucose uptake during postprandial hyperglycemia³². In the present study, the increase in lean body mass with higher maternal BMI may be a protective factor for glucose intolerance. On the other hand, type 2 diabetes is also associated with an excessive loss of skeletal muscle mass, hence complicating the interpretation of the results³³.

We observed different outcomes in men and women. There are sex differences in the development of type 2 diabetes and men are diagnosed with diabetes at a lower age and with a lower BMI than women³⁴. In mice, maternal high fat diet leads to higher oxidative stress in beta cells in male offspring, and in female offspring, estradiol seems to protect from oxidative stress³⁵. Additionally, sex differences are well reported in previous studies regarding maternal obesity and offspring later health³⁶.

Our findings provide novel information about the long-term effects of maternal BMI on glucose metabolism in the offspring. Obesity in pregnant women has increased in prevalence globally, resulting in an urgent need to better understand the long-term consequences of maternal obesity². Further understanding of these associations may improve primary prevention of obesity in young women and, consequently, of cardiometabolic outcomes in the offspring.

In conclusion, we have studied the association between maternal BMI and glucose and insulin metabolism in non-diabetic offspring in adult life. Our main finding is that a high maternal BMI was associated with better glucose tolerance in non-obese men. The results may in part be explained by the increase in lean body mass, which may be a protective factor for glucose intolerance. This study gives further insight in the complex associations between maternal adiposity and offspring cardiometabolic outcomes later in life.

Duality of interest

Authors report no conflict of interest.

Funding

HBCS was supported by Emil Aaltonen Foundation, Finnish Foundation for Cardiovascular Research, Finnish Foundation for Diabetes Research, Finnish Foundation for Pediatric Research, Juho Vainio Foundation, Novo Nordisk Foundation, Signe and Ane Gyllenberg Foundation, Samfundet Folkhälsan, Finska Läkaresällskapet, Liv och Hälsa, European Commission FP7 (DORIAN) grant agreement no 278603 and EU H2020-PHC-2014-DynaHealth grant no. 633595. The Academy of Finland supported MBvB (grant no. 257239), EK (grant no. 127437, 129306, 130326, 134791 and 2639249) JGE (grant no. 129369, 129907, 135072, 129255 and 126775).

Journal Pre-proofs

References

1. Afshin A, Forouzanfar MH, Reitsma MB, et al. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. *The New England journal of medicine*. 2017;377(1):13-27.
2. Poston L, Caleyachetty R, Cnattingius S, et al. Preconceptional and maternal obesity: epidemiology and health consequences. *The lancet Diabetes & endocrinology*. 2016;4(12):1025-1036.
3. Norman JE, Reynolds RM. The consequences of obesity and excess weight gain in pregnancy. *The Proceedings of the Nutrition Society*. 2011;70(4):450-456.
4. Chu SY, Callaghan WM, Kim SY, et al. Maternal obesity and risk of gestational diabetes mellitus. *Diabetes care*. 2007;30(8):2070-2076.
5. O'Brien TE, Ray JG, Chan WS. Maternal body mass index and the risk of preeclampsia: a systematic overview. *Epidemiology (Cambridge, Mass)*. 2003;14(3):368-374.
6. Godfrey KM, Reynolds RM, Prescott SL, et al. Influence of maternal obesity on the long-term health of offspring. *The lancet Diabetes & endocrinology*. 2017;5(1):53-64.
7. Alfaradhi MZ, Ozanne SE. Developmental programming in response to maternal overnutrition. *Frontiers in genetics*. 2011;2:27.
8. Ford SP, Zhang L, Zhu M, et al. Maternal obesity accelerates fetal pancreatic beta-cell but not alpha-cell development in sheep: prenatal consequences. *American journal of physiology Regulatory, integrative and comparative physiology*. 2009;297(3):R835-843.
9. Taylor PD, Samuelsson AM, Poston L. Maternal obesity and the developmental programming of hypertension: a role for leptin. *Acta physiologica (Oxford, England)*. 2014;210(3):508-523.
10. Sharp GC, Lawlor DA, Richmond RC, et al. Maternal pre-pregnancy BMI and gestational weight gain, offspring DNA methylation and later offspring adiposity: findings from the Avon Longitudinal Study of Parents and Children. *International journal of epidemiology*. 2015;44(4):1288-1304.
11. Gaillard R, Steegers EA, Duijts L, et al. Childhood cardiometabolic outcomes of maternal obesity during pregnancy: the Generation R Study. *Hypertension (Dallas, Tex : 1979)*. 2014;63(4):683-691.
12. Perng W, Gillman MW, Mantzoros CS, Oken E. A prospective study of maternal prenatal weight and offspring cardiometabolic health in midchildhood. *Annals of epidemiology*. 2014;24(11):793-800.e791.
13. Catalano PM, Farrell K, Thomas A, et al. Perinatal risk factors for childhood obesity and metabolic dysregulation. *The American journal of clinical nutrition*. 2009;90(5):1303-1313.
14. Gaillard R, Steegers EA, Franco OH, Hofman A, Jaddoe VW. Maternal weight gain in different periods of pregnancy and childhood cardio-metabolic outcomes. The Generation R Study. *International journal of obesity (2005)*. 2015;39(4):677-685.
15. Hochner H, Friedlander Y, Calderon-Margalit R, et al. Associations of maternal prepregnancy body mass index and gestational weight gain with adult offspring cardiometabolic risk factors: the Jerusalem Perinatal Family Follow-up Study. *Circulation*. 2012;125(11):1381-1389.
16. Reynolds RM, Osmond C, Phillips DI, Godfrey KM. Maternal BMI, parity, and pregnancy weight gain: influences on offspring adiposity in young adulthood. *The Journal of clinical endocrinology and metabolism*. 2010;95(12):5365-5369.
17. Rooney BL, Mathiason MA, Schauburger CW. Predictors of obesity in childhood, adolescence, and adulthood in a birth cohort. *Maternal and child health journal*. 2011;15(8):1166-1175.
18. Kaseva N, Vaarasmaki M, Matinolli HM, et al. Pre-pregnancy overweight or obesity and gestational diabetes as predictors of body composition in offspring twenty years later: evidence from two birth cohort studies. *International journal of obesity (2005)*. 2018;42(4):872-879.
19. Reynolds RM, Allan KM, Raja EA, et al. Maternal obesity during pregnancy and premature mortality from cardiovascular event in adult offspring: follow-up of 1 323 275 person years. *BMJ (Clinical research ed)*. 2013;347:f4539.
20. Eriksson JG, Sandboge S, Salonen MK, Kajantie E, Osmond C. Long-term consequences of maternal overweight in pregnancy on offspring later health: findings from the Helsinki Birth Cohort Study. *Ann Med*. 2014;46(6):434-438.
21. Tabak AG, Jokela M, Akbaraly TN, Brunner EJ, Kivimaki M, Witte DR. Trajectories of glycaemia, insulin sensitivity, and insulin secretion before diagnosis of type 2 diabetes: an analysis from the Whitehall II study. *Lancet (London, England)*. 2009;373(9682):2215-2221.

22. Mosteller RD. Simplified calculation of body-surface area. *The New England journal of medicine*. 1987;317(17):1098.
23. Eriksson JG, Sandboge S, Salonen M, Kajantie E, Osmond C. Maternal weight in pregnancy and offspring body composition in late adulthood: findings from the Helsinki Birth Cohort Study (HBCS). *Ann Med*. 2015;47(2):94-99.
24. Lakka TA, Venalainen JM, Rauramaa R, Salonen R, Tuomilehto J, Salonen JT. Relation of leisure-time physical activity and cardiorespiratory fitness to the risk of acute myocardial infarction. *The New England journal of medicine*. 1994;330(22):1549-1554.
25. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organization technical report series*. 2000;894:i-xii, 1-253.
26. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes care*. 2004;27(6):1487-1495.
27. Shokry E, Marchioro L, Uhl O, et al. Impact of maternal BMI and gestational diabetes mellitus on maternal and cord blood metabolome: results from the PREOBE cohort study. *Acta diabetologica*. 2019.
28. Pintaudi B, Fresa R, Dalfra M, et al. The risk stratification of adverse neonatal outcomes in women with gestational diabetes (STRONG) study. *Acta diabetologica*. 2018;55(12):1261-1273.
29. Yliharsila H, Kajantie E, Osmond C, Forsen T, Barker DJ, Eriksson JG. Birth size, adult body composition and muscle strength in later life. *International journal of obesity (2005)*. 2007;31(9):1392-1399.
30. Srikanthan P, Karlamangla AS. Relative muscle mass is inversely associated with insulin resistance and prediabetes. Findings from the third National Health and Nutrition Examination Survey. *The Journal of clinical endocrinology and metabolism*. 2011;96(9):2898-2903.
31. Larsen BA, Wassel CL, Kritchevsky SB, et al. Association of Muscle Mass, Area, and Strength With Incident Diabetes in Older Adults: The Health ABC Study. *The Journal of clinical endocrinology and metabolism*. 2016;101(4):1847-1855.
32. Meyer C, Dostou JM, Welle SL, Gerich JE. Role of human liver, kidney, and skeletal muscle in postprandial glucose homeostasis. *American journal of physiology Endocrinology and metabolism*. 2002;282(2):E419-427.
33. Park SW, Goodpaster BH, Lee JS, et al. Excessive loss of skeletal muscle mass in older adults with type 2 diabetes. *Diabetes care*. 2009;32(11):1993-1997.
34. Logue J, Walker JJ, Colhoun HM, et al. Do men develop type 2 diabetes at lower body mass indices than women? *Diabetologia*. 2011;54(12):3003-3006.
35. Yokomizo H, Inoguchi T, Sonoda N, et al. Maternal high-fat diet induces insulin resistance and deterioration of pancreatic beta-cell function in adult offspring with sex differences in mice. *American journal of physiology Endocrinology and metabolism*. 2014;306(10):E1163-1175.
36. Gabory A, Attig L, Junien C. Sexual dimorphism in environmental epigenetic programming. *Molecular and cellular endocrinology*. 2009;304(1-2):8-18.

Table 1. Maternal and neonatal characteristics according to quartiles of maternal body mass index during late pregnancy. Data are presented as mean (SD) or number (%).

Characteristics	Maternal body mass index group				P for trend
	I N=357	II N=363	III N=359	IV N=361	
BMI, (kg/m ²), range	<24.6	24.6-26.2	26.3-28.0	>28.0	
Maternal					
Age (years)	27.3 (5.2)	28.0 (5.4)	28.8 (5.3)	30.4 (5.5)	<0.001
Weight (kg)	60.0 (4.6)	64.9 (4.9)	69.4 (5.2)	76.1 (6.7)	<0.001
Length (cm)	160.5 (6.1)	159.8 (5.9)	159.8(6.0)	158.6 (5.4)	<0.001
BSA [†] (m ²)	1.63 (0.09)	1.70 (0.09)	1.75 0.10)	1.83 (0.10)	<0.001
Parity	1.6 (1.0)	1.8 (1.2)	2.0 (1.3)	2.2 (1.5)	<0.001
Neonatal					
Boys, n (%)	163 (46)	178 (49)	142 (40)	153 (42)	0.10
Gestational age (weeks)	39.8 (1.6)	40.0 (1.6)	40.0 (1.5)	40.2 (1.5)	0.003
Weight (g)					
Boys	3280 (474)	3471 (422)	3605(427)	3630 (509)	<0.001
Girls	3178 (443)	3380 (448)	3411(441)	3521 (460)	<0.001
Length (cm)					
Boys	49.9 (2.3)	50.7 (1.7)	51.0 (1.9)	51.2 (1.9)	<0.001
Girls	49.5 (1.9)	50.1 (1.9)	50.2 (1.8)	50.5 (1.7)	<0.001
Ponderal index (kg/m ³)					
Boys	26.2 (2.2)	26.5 (2.1)	27.1 (2.8)	26.9 (2.3)	0.003
Girls	26.0 (2.0)	26.8 (2.2)	26.9 (2.0)	27.3 (2.4)	<0.001

[†]Calculated with Mosteller formula

BMI Body Mass Index, *BSA* Body Surface Area

Table 2. Adult offspring anthropometry and clinical characteristics for men and women according to quartiles of maternal body mass index during late pregnancy. Data are presented as mean (SD) or number (%).

Characteristics	Maternal body mass index group				P for trend
	I (<24.6)	II (24.6- 26.2)	III (26.3- 28.0)	IV (>28.0)	
Women, n	194	185	217	208	
Age (years)	62 (3)	62 (3)	61 (3)	61 (3)	0.17
Height (cm)	163 (6)	163 (6)	164 (6)	163 (5)	0.62
Weight (kg)	70.0 (11.5)	72.5 (12.4)	72.8 (13.5)	75.1 (14.2)	<0.001
BMI (kg/m ²)	26.3 (4.1)	27.2 (4.4)	27.0 (4.7)	28.4 (5.4)	<0.001
Waist (cm)	88 (10)	89 (12)	89 (13)	92 (13)	<0.001
Current smokers, n (%)	41 (21)	38 (21)	50 (23)	46 (22)	0.68
Lean body mass (kg)	46.1(5.3)	47.6(5.3)	48.0(5.8)	47.9(5.2)	<0.001
Fat %	33.0(6.5)	33.0(6.6)	32.8(7.0)	34.8(7.3)	0.016
BSA [†]	1.78(0.16)	1.81(0.16)	1.82(0.18)	1.83(0.18)	<0.001
LTPA (met/wk)	46.5 (34.8)	48.8 (37.8)	44.9 (40.7)	46.2 (49.0)	0.73
Blood pressure (mmHg)					
Systolic	144 (21)	142 (20)	142 (20)	143 (22)	0.96
Diastolic	88 (9)	87 (11)	87 (10)	88 (11)	0.98
Cholesterol (mmol/L)	6.16 (1.08)	6.18 (0.95)	6.12 (1.00)	6.09 (1.01)	0.42
LDL-cholesterol (mmol/L)	3.72 (0.94)	3.80 (0.82)	3.74 (0.88)	3.77 (0.89)	0.76
HDL-cholesterol (mmol/L)	1.79 (0.43)	1.77 (0.47)	1.77 (0.42)	1.70 (0.39)	0.041
Triglycerides (mmol/L)	1.47 (0.77)	1.35 (0.70)	1.34 (0.70)	1.41 (0.73)	0.43
hs-CRP (mg/L)	3.33 (4.99)	3.68 (5.58)	3.05 (4.14)	3.16 (5.06)	0.46
Men, n	163	178	142	153	
Age (years)	62 (3)	61 (3)	61 (3)	62 (3)	0.80
Height (cm)	176 (6)	177 (6)	177 (6)	177 (6)	0.16
Weight (kg)	82.3 (11.8)	84.8 (12.2)	84.6 (13.2)	85.9 (13.8)	0.021
BMI (kg/m ²)	26.6 (3.4)	27.0 (3.6)	26.9 (3.9)	27.4 (4.0)	0.069
Waist (cm)	98 (9)	99 (10)	99 (11)	101 (12)	0.11
Current smokers, n (%)	37 (23)	50 (28)	51 (36)	61 (40)	<0.001
Lean body mass (kg)	62.8(7.2)	64.7(7.5)	65.1(7.9)	65.0(8.0)	0.009
Fat %	23.1(5.1)	23.1(5.4)	22.3(6.3)	23.7(5.6)	0.54
BSA [†]	2.00(0.16)	2.04(0.16)	2.03(0.17)	2.05(0.18)	0.021
LTPA (met/wk)	49.3 (40.1)	46.0 (47.4)	41.8 (34.4)	45.9 (36.4)	0.30
Blood pressure (mmHg)					
Systolic	147 (18)	146 (20)	144 (20)	144 (18)	0.087
Diastolic	90 (9)	91 (10)	90 (11)	89 (11)	0.25
Cholesterol (mmol/L)	5.75 (1.04)	5.84 (1.07)	5.91 (0.99)	5.81 (1.03)	0.55
LDL-cholesterol (mmol/L)	3.62 (0.89)	3.68 (0.88)	3.73 (0.79)	3.64 (0.84)	0.72
HDL-cholesterol (mmol/L)	1.45 (0.34)	1.49 (0.36)	1.51 (0.41)	1.49 (0.43)	0.32
Triglycerides (mmol/L)	1.55 (0.78)	1.47 (0.77)	1.48 (0.78)	1.46 (0.74)	0.35
hs-CRP (mg/L)	2.90 (4.43)	2.56 (3.52)	2.49 (3.25)	3.81(7.66)	0.22

[†]Calculated with Mosteller formula

BMI Body Mass Index, *BSA* Body Surface Area, *LTPA* Leisure Time Physical Activity, *MET* Metabolic Equivalent of Task, *Hs-CRP* High sensitive C-reactive protein

Figure 1. Fasting (FPG) and 2-hour plasma glucose (2hPG) according to quartiles of maternal body mass index during late pregnancy in men and women in different adulthood body mass index groups (values adjusted for age, BMI, smoking and LTPA).

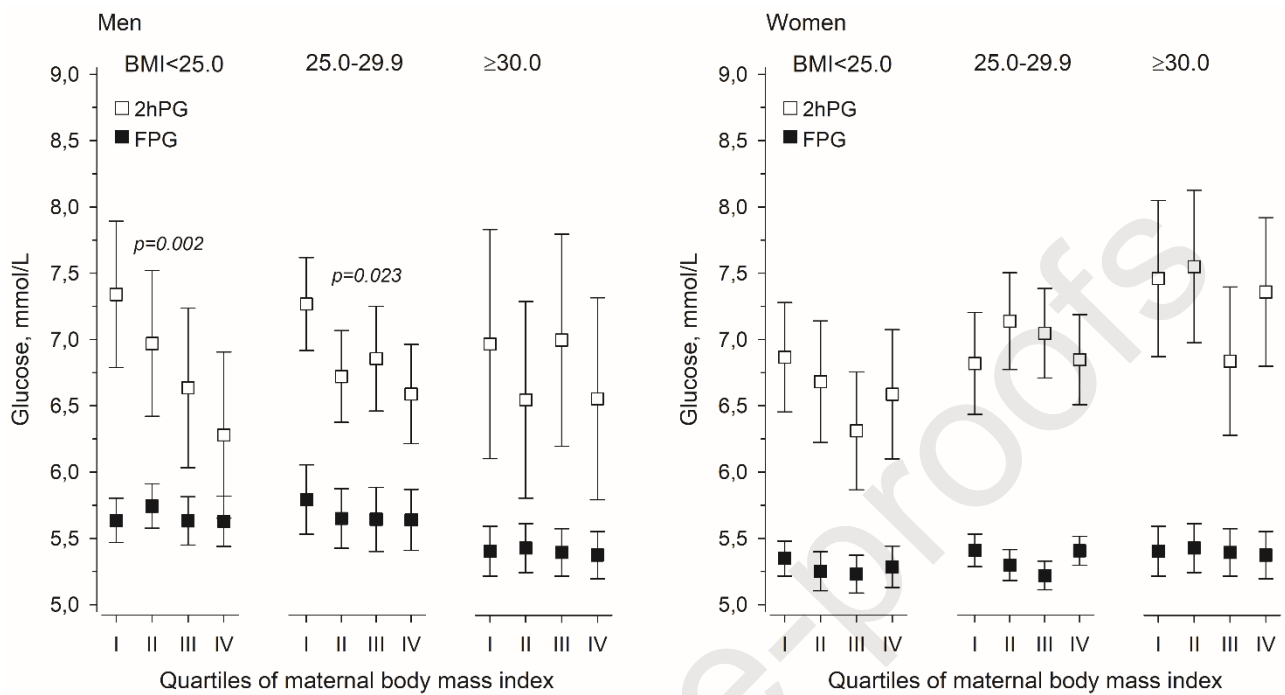


Figure 2. HOMA-IR according to quartiles of maternal body mass index in late pregnancy in men and women in different adulthood body mass index groups (values adjusted for age, BMI, smoking and LTPA).

