**Leptin and insulin in young adulthood are associated with weight in infancy**

**Umberto Simeoni1\*, Clive Osmond2, Ricardo Garay3, Christophe Buffat4,**

**Farid Boubred5, Christophe Chagnaud6, Elisabeth Jouve7,**

**Christine Audebert7, Jean-Michel Antoine8, Kent Thornburg9.**

**1**Division of Pediatrics & DOHaD Laboratory, CHUV University Hospital and University of Lausanne, Switzerland

**2**MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, United Kingdom

**3**Craven, Villemoisson-sur-Orge, France

**4** Laboratoire de Biochimie et de Biologie Moléculaire, Hôpital de la Conception, Marseille, France

**5**Division of Neonatology, Assistance Publique, Hôpitaux de Marseille, France

**6**Division of Radiology and Medical imaging, Assistance Publique, Hôpitaux de Marseille, France

**7**UPCET, Clinical Pharmacology, Assistance Publique, Hôpitaux de Marseille, France

**8**Danone Institute International, Paris, France

**9**Bob and Charlee Moore Institute for Nutrition and Wellness, Oregon Health & Science University, Portland, Oregon, United States

FOOTNOTES

**Abbreviations:** BMI, Body mass index; CV, cardiovascular; HOMA, Homeostasis Model Assessment; MI, myocardial infarction; T2DM, type 2 diabetes Mellitus

**Running head (short title):** Leptin programming

\*Correspondence to Prof. Umberto Simeoni, Division of Pediatrics & DOHaD Laboratory, CHUV University Hospital and UNIL, Lausanne, Switzerland (e-mail: Umberto.Simeoni@chuv.ch)

**ABSTRACT**

Low weight in early infancy is a known risk factor for cardio-metabolic syndrome in adult life. However, little is known either about developmental programming in subjects of normal birthweight, or about events between the ages which separate early programming and the occurrence of disease at late adulthood. We tested the hypothesis that circulating concentrations of leptin, adiponectin and insulin in young, healthy adults, born with a birth size within the normal range, are influenced by early life growth patterns. In an observational study of 188 healthy volunteers aged 18 to 25 years (97 males, 91 females) we investigated the association of metabolic function with their birth size, their growth during childhood and their body composition. High plasma leptin in early adulthood, a risk factor for cardio-metabolic syndrome, was associated with low weight at age two years (correlation coefficient controlled for adult weight = -0.21, p<0.01). It was also positively associated with pre-prandial insulin and with HOMA (Homeostasis Model Assessment) insulin resistance. Leptin, leptin-adiponectin ratio and insulin correlated with lean mass, fat mass and percent fat (p< 0.0001). In conclusion, high leptin in early adulthood was associated with both low weight at age two years and insulin resistance. We speculate that high leptin is developmentally programmed and can contribute to the association between low weight in early infancy and increased cardio-metabolic risk in adulthood in heathy subjects.

Keywords: birth weight; coronary artery disease; diabetes; metabolic syndrome; leptin; adiponectin; percentage fat.

**INTRODUCTION**

Twenty-five years of evidence associate early nutrition and growth patterns during pregnancy, early infancy and the pre-conception period, with an elevated risk for chronic disease in later life, including cardiovascular disease and type 2 diabetes mellitus (T2DM). Barker and colleagues (Barker, et al. 1989) first reported an inverse relationship between birthweight, weight at one year and risk of coronary heart disease among adults born in Hertfordshire, UK. They also found that low weight at the age of one year was associated with an increased risk for metabolic disease (Barker, et al. 1993) and left ventricular hypertrophy in adulthood (Vijayakumar, et al. 1995). The process by which early life stressors impart risk for adult-onset disease is known as programming but its biological underpinnings are not completely understood.

The risk of coronary events has been found to be related to low weight at birth and during infancy, followed by a rapid increase in body mass index (BMI) after the age of 2 years (Barker, et al. 2005). This pattern of childhood growth was associated with insulin resistance in later life.

The close link between T2DM and eventual cardiovascular disease (Grundy, et al. 1999; Manson, et al. 1991) led Hales and Barker to propose the “thrifty phenotype” hypothesis (Hales and Barker 2001), which provided a common origin for the two diseases. They suggested that sub-optimal fetal growth, associated with maternal malnutrition, programs an individual to be vulnerable for the metabolic syndrome (T2DM, high plasma triglycerides, low HDL cholesterol and hypertension) (Barker 2000).

Low birthweight babies have decreased muscle mass in infancy (Robinson and Wheeler T 1991), a condition maintained throughout life which makes them vulnerable for metabolic disease (Baker, et al. 2010). Rapid growth of adolescents who were born small or prematurely is associated with endothelial dysfunction (Ligi, et al. 2011; Singhal, et al. 2004) and ischemic heart disease (Eriksson, et al. 1999). Animal studies have characterized the role of nutrition during gestation and the early postnatal period in the later development of cardio-vascular and metabolic disorders at adulthood (Boubred, et al. 2007; Siddeek, et al. 2018; Yzydorczyk, et al. 2017). Thus, one could reasonably expect that the regulation of metabolic hormones in adulthood is related to growth patterns during prenatal and early postnatal life. Variations of birth weight within the normal range have been shown to be sufficient to influence the cardio-metabolic risk (Barker et al. 1989). However little is known on developmental programming that occurs under the influence of variations in what is considered the normal environment, and on the time sequence across the period of the life course which separates early programming and the occurrence of disease at late adulthood.

Adipokines, such as leptin and adiponectin, and the pancreatic hormone, insulin work in harmony to regulate appetite and a number of metabolic processes through their receptors. Leptin is best known as a powerful suppressor of appetite (Halaas, et al. 1995) in people who have normal weight control but is elevated in people with a large fat mass (Friedman and Mantzoros 2015). When found in high concentrations leptin is associated with a number of adverse cardiovascular conditions including generalized inflammation (Otero, et al. 2005) and endothelial dysfunction (Sweeney 2010). While circulating concentrations of leptin are generally proportional to body fat mass (Yang and Barouch 2007), adiponectin concentrations are known to be depressed in people who have a body mass index that exceeds 30 kg/m2 (Lihn, et al. 2005). Plasma concentrations of adiponectin are inversely related to systolic blood pressure (Huang, et al. 2003) as well as to insulin resistance (Bacha, et al. 2004). The ratio between circulating concentrations of leptin and adiponectin has been used as a marker for adverse outcomes in people at risk for diabetes and metabolic disease (Satoh, et al. 2004). The ratio also correlates with the homeostasis model assessment of insulin resistance (HOMA-IR) during pregnancy (Skvarca, et al. 2013). Therefore, all three hormones are related to metabolic health and when abnormal lead to cardiovascular disease.

Leptin is known to have an important role in developmental programming. Early life hyperleptinemia has been shown to affect the hardwiring of developing CNS, particularly hypothalamic appetite regulation areas, and the cardio-vascular sympathetic drive (Taylor, et al. 2014). In contrast, neonatal leptin treatment has been shown to reverse altered developmental programming induced by fetal undernutrition in rodents (Vickers, et al. 2005).

We sought to test the hypothesis that circulating concentrations of leptin, adiponectin and insulin in young, healthy adults, born with a birth size within the normal range, are influenced by early life growth patterns among normal young adults. To test the hypothesis, we sought to evaluate the relationship between birth size and growth patterns during childhood and the circulating concentrations of leptin, adiponectin and insulin young in 22 year old university students. We studied 188 normal young men and women whose birth size, infant and childhood growth data had been recorded in their personal health records (the “carnet de santé”).

**SUBJECTS, METHODS**

*Subjects*. We performed an observational study in 188 healthy volunteers, aged 18 to 25 years, recruited at the Centre de Médecine Préventive at Aix-Marseille Université, and at the Center for Clinical Investigation (UPCET) at Assistance-Publique Hôpitaux de Marseille, France. They had to be registered in the French Social Security system, and to have growth data in their health records, including height and weight at birth, 4 months, 9 months, 2 years, 6 years and 12 years of age. The study was approved by the Comité de Protection des Personnes n°2 (Marseille, France) ethical review board. Subjects signed a consent form for the study. Subjects were excluded if they were born preterm, small for gestational age, had congenital heart disease, chronic endocrine or renal disease, metabolic disease acquired in childhood, non-idiopathic hypertension, non-idiopathic obesity, malignant disease or were pregnant. Subjects were typically students at the Faculty of Medicine, Aix-Marseille University.

*Assessments.* The following measurements were made at UPCET, over a two- day time period.

*Anthropometry.* Height and weight at birth, 4 months, 9 months, 2 years, 6 years, 12 years of age were recorded from the subject’s personal health care booklet. Height, weight, waist and hip circumferences were measured at the visit using a calibrated scale. Body Mass Index (BMI, weight/height2) and waist/hip ratio were derived.

*Body composition*. Total and regional (upper limbs, trunk, lower limbs) lean mass and fat mass were measured using Dual Energy X-Rays Absorptiometry (DEXA) whole body scanning (DXA; Hologic, Bedford, MA, USA).

*Biochemical parameters:* Venous blood samples were collected after an overnight (≥12 h) fast and 2 hours after a standardised breakfast. The samples were centrifuged at +4° C, aliquoted and immediately frozen for future analysis. Blood samples were also analysed for concentrations of plasma glucose, triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), insulin, adiponectin, leptin, homocysteine, ultrasensitive C-reactive protein and folic acid. Serum lipids (enzymatic methods) and plasma glucose (glucose oxidase method) were assayed using the UniCel DxC 600 automatic biochemistry analysis system (Beckman, CA). HDL-C was measured directly. LDL-C(mmol/l) was estimated using Friedewald's formula as {TC (mmol/l) – HDL-C(mmol/l) - TG(mmol/l)/2.2}. Adiponectin and leptin concentrations were measured by ELISA according to the manufacturer’s instructions (R & D System, USA; SPI-Bio, France respectively) and Insulin was determined by Electrochemiluminescence (ECL) technology (Roche, Germany).

*Statistics.*

*Descriptive Statistics.* We used means and standard deviations as descriptive statistics for symmetrically distributed variables. We used medians and quartiles to describe variables that were skewed, and log transformation for their analysis (Tables 1, 2).

*Measurement of association*. We measured the strength of association among metabolic measures and with weight at each age by using partial correlation coefficients, for which control was made for sex and for adult age and sometimes weight (Tables 3, 4, 7). We also used tabulation of mean values according to groups of growth and adult size to illustrate these results (Table 6).

*Growth*. We expressed growth in weight in the interval from birth to age two years using the conditional approach. In this the residual from the sex-specific regression of weight at age two years on birth weight is expressed as a standardized score. This measure expresses growth in infancy beyond that predicted from birth size, with which it is statistically uncorrelated. We then analysed outcomes using a regression model which included sex, adult age, birth weight, infant growth and adult weight as the predictors (Table 5). As an alternative approach we used principal component analysis to identify the three most varying characteristic of the full set of growth measures, and used these components in regression models (supplementary material).

*Multiple testing*. To control the number of possible false positive associations we used Bonferroni correction of p-values in each analysis. The p-values required to declare statistical significance are given in the footnote to each Table.

**RESULTS**

We studied 188 subjects (97 males, 91 females) aged around 22 years. Their body size at birth, 4m, 9m, 2y, 6y, 12y and in adult life is described in Table 1 and illustrated in Figure 1 using WHO standards for comparison. As expected, differences in size between sexes arose after puberty, with higher lean mass and lower percent fat in males. Birth weight was below 2.5kg for 2% of males and 7% of females, and above 4 kg for 3% and 7%, respectively. Body mass index (BMI, kg/m2) in adulthood was below 20 in 11% and 42%; between 20 and 25 in 73% and 55% and above 25 in 15% and 3% respectively. None had a BMI above 30.

Descriptive data for pre- and post-prandial plasma measurements are shown in Table 2. Mean plasma concentrations of leptin, adiponectin, insulin and C-peptide were higher in females than in males.

Adult leptin and adiponectin concentrations, their ratio and insulin concentration were associated with adult measures of body composition. The top half of Table 3 shows that, controlling for age and sex, leptin and its ratio were positively associated with current weight, BMI, fat mass, percent fat, waist and hip circumferences and trunk fat mass. The strongest associations were with percent fat. Adiponectin concentration was not significantly associated with adult body composition measures, but insulin was associated with fat mass, percent fat and fat mass. When further controlling for current weight, leptin and its ratio were also negatively associated with height and lean mass. Again, adiponectin was not significantly associated with any measure of body composition.

As shown in Figure 2 the relationship between circulating leptin concentrations and fat mass was different for men and women. Women had higher concentrations for each kg of fat mass than men. Log leptin increased by 0.131 (95% confidence interval 0.106 to 0.157) per kg of fat mass in men, but only by 0.087 (0.064 to 0.109) in women (p for difference = 0.008). However, when fat mass was expressed as a percentage of body weight, leptin concentrations were linearly associated with percent fat in both sexes, with women’s concentrations and percentages of fat generally at the higher end of the curve (Figure 2). Log leptin concentration increased by 0.126 (0.104 to 0.149) per unit of percentage fat in men and by 0.103 (0.082 to 0.124) in women (p for difference = 0.12).

Table 4 shows the associations of weights at birth and at ages through to adulthood with adult leptin and adiponectin concentrations, their ratio and insulin concentration . In the top half of the table, adjustments were made for the subject’s adult age and sex. Leptin concentrations and its ratio to adiponectin were only associated with adult weight. Further adjusting for current adult weight, as in the bottom half of the Table, leptin and its ratio were negatively associated with the subjects’ weight at age two years and, more weakly at age six years.

Table 5 shows regression models for leptin, adiponectin, their ratio and insulin in which the individual’s growth trajectory is expressed by birth size, conditional infant growth and adult size. Leptin and the ratio were significantly negatively associated with both adult weight and with infant growth. The pattern for insulin was similar but a little weaker. That with adiponectin was weaker still and in the reverse direction.

Results from an alternative approach based on principal component analysis of all the weights are given in the supplementary material. These analyses highlight the specificity of the early changes in weight in the prediction of leptin, adiponectin, their ratio and insulin concentration. Measures that are based on average weights or linear trends in weight, for example, are much less predictive.

Table 6 illustrates how values of the leptin/adiponectin ratio vary according to sex-specific thirds of weight at age two years and adult weight. For males and for females the ratio tends to increase along the rows of the table as adult weight increases, but decreases down the columns as weight at age two years increases. A further illustration is given in Figure 3, which shows how leptin, adiponectin and their ratio, when controlled by regression for sex, adult age and weight at their mean values, are associated with weight at age two years, which is divided into fifths.

In Table 7 we explore the associations of leptin and adiponectin concentrations with measures related to glucose regulation: insulin, HOMA-IR, C-peptide and with lipid concentrations. Adjusting for adult age and sex in the top half of the Table, leptin and the ratio are positively associated with pre-prandial insulin and C-peptide and with HOMA insulin resistance. Adiponectin is positively associated with HDL cholesterol concentration. Further adjustment for percent fat in the bottom half of the Table tends to attenuate these associations, but not to change the overall pattern.

**DISCUSSION**

Previous studies have been designed to determine the degree to which low body weight in infancy is associated with elevated risk of metabolic disease, including insulin resistance and type 2 diabetes, in adult life. In contrast, this study was designed to determine whether the regulation of metabolic hormones in healthy 22 year old subjects was associated with growth patterns throughout childhood, with the aim of better understanding the natural history of developmentally programmed regulations. We investigated three important regulators of metabolism; adipose-derived leptin and adiponectin and pancreatic insulin. The primary finding of the study is that plasma concentrations of leptin as well as of insulin in young, healthy adults may be developmentally programmed.

We found that leptin and insulin at adulthood in young adult life are negatively correlated with weight at 2 years of age when adjusted for age, sex and current weight (Tables 4-6 and Figure 3). Thus, 22 year old men and women had higher concentrations of leptin and insulin if they had low body weight as two year olds. This finding may have high physiologic significance, because the effect size is similar to that of increasing body weight at young adulthood (Table 6). This suggests that the regulatory “set points” for both circulating leptin and insulin concentrations are determined in early childhood.

We speculate that these findings have important implications:

1. Several aspects of metabolic control in young adults are associated with the nutritional environments of those individuals between birth and late infancy.
2. The propensity for the subjects in this study to acquire chronic diseases in later life may also relate to their growth patterns in childhood. If true, this finding represents another physiological link between early life growth and later life disease. Proof of this speculation will require studies of these subjects in future years.

As expected, each of the anatomic constituents related to body fat mass is correlated with leptin concentrations (Table 3). Previous studies have shown that high leptin concentrations are a risk factor for cardiovascular disease, irrespective of obesity (Koh, et al. 2008). In the West of Scotland Coronary Prevention Study leptin was an independent risk factor for coronary heart disease (Wallace, et al. 2001). Moreover, high leptin concentrations have been found in patients with first-ever myocardial infarction (Söderberg, et al. 1999), in acute ST segment elevation myocardial infarction (Jose, et al. 2005; Taneli, et al. 2006) and in hypertensive patients with myocardial infarction (Wallerstedt, et al. 2004). We speculate that the concentrations of leptin that exceed those expected by their fat mass are associated with later cardiovascular and metabolic disease risk.

We found that women have leptin concentrations that exceed those of men, even out of proportion to their larger fat mass, suggesting that adipose tissue releases more leptin per gram in women than in men. This is not a new finding. However, it is interesting to note that leptin concentrations are more closely associated with percent body fat in young healthy adults than to fat mass itself. This fact, together with the inverse relationship between leptin concentrations and two year old weight, suggests that the regulation of leptin in the circulation blood of healthy, 22 year olds may be acting through the programming of body composition in early childhood. This may occur as a consequence of the low infant fat intakes which characterize the nutrition in early infancy of certain subjects who tend to develop overweight or obesity as young adults, as shown in a prospective cohort study in France (Rolland-Cachera, et al. 2013).

Moreover, we found high leptin associated with high C-peptide concentration, which may be involved in the mechanism of central lipid resistance (Koh et al. 2008).

Adiponectin concentrations were unrelated to fat mass in either males or females, as seen by others (Baratta, et al. 2004). However, concentrations in young adults were positively correlated with weight at four months and six years. A low concentration of adiponectin is an independent risk factor for developing the metabolic syndrome (Renaldi, et al. 2009) and T2DM (Hara, et al. 2005 ; Vasseur, et al. 2006). Therefore, our finding of low adiponectin associated with low weight at age two years deserves further investigation.

Several limitations of this study should be taken into consideration. The study is observational and does not allow a causal inference. Potential known or unknown confounding factors, such as educational level, dietary factors and physical activity may have altered the study findings. Alternative causal patterns, not involving confounders, can explain our observations.

In conclusion, this study suggests that plasma leptin concentration is programmed during early life as revealed in normal young men and women, when the rates of chronic disease are low. This may further explain the correlation between low weight in early infancy and increased risk of coronary heart disease in adulthood (Barker et al. 1989; Zohdi, et al. 2014). High leptin can be one important etiological factor for the early origin of cardio-metabolic syndrome in adult life (Zohdi et al. 2014).

**ACKNOWLEDGMENTS**

Authors contributed equally to the work.

This study was supported by an unrestricted grant from Danone Institute International, Paris, France.

This article is dedicated to the memory of Professor David JP Barker, the founder of the field of developmental origins of health and disease and a dear colleague to all of us.

Conflict of interest: none declared.

**REFERENCES**

Bacha F, Saad R, Gungor N & Arslanian SA 2004 Adiponectin in youth: relationship to visceral adiposity, insulin sensitivity, and beta-cell function. *Diabetes Care* **27** 547-552.

Baker J, Workman M, Bedrick E, Frey MA, Hurtado M & Pearson O 2010 Brains versus brawn: an empirical test of Barker's brain sparing model. *Am J Hum Biol* **22** 206-215.

Baratta R, Amato S, Degano C, Farina MG, Patanè G, Vigneri R & Frittitta L 2004 Adiponectin relationship with lipid metabolism is independent of body fat mass: evidence from both cross-sectional and intervention studies. *J Clin Endocrinol Metab* **89** 2665-2671.

Barker DJ 2000 In utero programming of cardiovascular disease. *Theriogenology* **53** 555-574.

Barker DJ, Hales CN, Fall CH, Osmond C, Phipps K & Clark PM 1993 Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. *Diabetologia* **36** 62-67.

Barker DJ, Osmond C, Forsén TJ, Kajantie E & Eriksson JG 2005 Trajectories of growth among children who have coronary events as adults. *N Engl J Med* **353** 1802-1809.

Barker DJP, Osmond C, Winter PD, Margetts B & Simmonds SJ 1989 Weight in infancy and death from ischaemic heart disease. *The Lancet* **334** 577-580.

Boubred F, Buffat C, Feuerstein JM, Daniel L, Tsimaratos M, Oliver C, Lelièvre-Pégorier M & Simeoni U 2007 Effects of early postnatal hypernutrition on nephron number and long-term renal function and structure in rats. *Am J Physiol Renal Physiol* **293** F1944-1949.

Eriksson JG, Forsén T, Tuomilehto J, Winter PD, Osmond C & Barker DJ 1999 Catch-up growth in childhood and death from coronary heart disease: longitudinal study. *BMJ* **318** 427-431.

Friedman JM & Mantzoros CS 2015 20 years of leptin: from the discovery of the leptin gene to leptin in our therapeutic armamentarium. *Metabolism* **64** 1-4.

Grundy SM, Benjamin IJ, Burke GL, Chait A, Eckel RH, Howard BV, Mitch W, Smith SC & Sowers JR 1999 Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation* **100** 1134-1146.

Halaas JL, Gajiwala KS, Maffei M, Cohen SL, Chait BT, Rabinowitz D, Lallone RL, Burley SK & Friedman JM 1995 Weight-reducing effects of the plasma protein encoded by the obese gene. *Science* **269** 543-546.

Hales CN & Barker DJ 2001 The thrifty phenotype hypothesis. *Br Med Bull* **60** 5-20.

Hara K, Yamauchi T & Kadowaki T 2005 Adiponectin: an adipokine linking adipocytes and type 2 diabetes in humans. *Curr Diab Rep* **5** 136-140.

Huang KC, Chen CL, Chuang LM, Ho SR, Tai TY & Yang WS 2003 Plasma adiponectin levels and blood pressures in nondiabetic adolescent females. *J Clin Endocrinol Metab* **88** 4130-4134.

Jose VJ, Mariappan P, George PV, Selvakumar & Selvakumar D 2005 Serum leptin levels in acute myocardial infarction. *Indian Heart J* **57** 39-43.

Koh KK, Park SM & Quon MJ 2008 Leptin and Cardiovascular Disease: Response to Therapeutic Interventions. *Circulation* **117** 3238-3249.

Ligi I, Simoncini S, Tellier E, Vassallo PF, Sabatier F, Guillet B, Lamy E, Sarlon G, Quemener C, Bikfalvi A, et al. 2011 A switch toward angiostatic gene expression impairs the angiogenic properties of endothelial progenitor cells in low birth weight preterm infants. *Blood* **118** 1699-1709.

Lihn AS, Pedersen SB & Richelsen B 2005 Adiponectin: action, regulation and association to insulin sensitivity. *Obes Rev* **6** 13-21.

Manson JE, Colditz GA, Stampfer MJ, Willett WC, Krolewski AS, Rosner B, Arky RA, Speizer FE & Hennekens CH 1991 A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. *Arch Intern Med* **151** 1141-1147.

Otero M, Lago R, Lago F, Casanueva FF, Dieguez C, Gómez-Reino JJ & Gualillo O 2005 Leptin, from fat to inflammation: old questions and new insights. *FEBS Lett* **579** 295-301.

Renaldi O, Pramono B, Sinorita H, Purnomo LB, Asdie RH & Asdie AH 2009 Hypoadiponectinemia: a risk factor for metabolic syndrome. *Acta Med Indones* **41** 20-24.

Robinson SM & Wheeler T HM, Barker DJ, Osmond C. . 1991 Dec;98(12):1223-7. 1991 Fetal heart rate and intrauterine growth. *Br J Obstet Gynaecol.* **98** 1223-1227.

Rolland-Cachera MF, Maillot M, Deheeger M, Souberbielle JC, Péneau S & Hercberg S 2013 Association of nutrition in early life with body fat and serum leptin at adult age. *Int J Obes (Lond)* **37** 1116-1122.

Satoh N, Naruse M, Usui T, Tagami T, Suganami T, Yamada K, Kuzuya H, Shimatsu A & Ogawa Y 2004 Leptin-to-adiponectin ratio as a potential atherogenic index in obese type 2 diabetic patients. *Diabetes Care* **27** 2488-2490.

Siddeek B, Li N, Mauduit C, Chehade H, Rigal E, Tolsa JF, Armengaud JB, Yzydorczyk C, Benahmed M, Vergely C, et al. 2018 Transient postnatal over nutrition induces long-term alterations in cardiac NLRP3-inflammasome pathway. *Nutr Metab Cardiovasc Dis* **28** 944-951.

Singhal A, Cole TJ, Fewtrell M, Deanfield J & Lucas A 2004 Is Slower Early Growth Beneficial for Long-Term Cardiovascular Health? *Circulation* **109** 1108-1113.

Skvarca A, Tomazic M, Blagus R, Krhin B & Janez A 2013 Adiponectin/leptin ratio and insulin resistance in pregnancy. *J Int Med Res* **41** 123-128.

Sweeney G 2010 Cardiovascular effects of leptin. *Nat Rev Cardiol* **7** 22-29.

Söderberg S, Ahrén B, Jansson JH, Johnson O, Hallmans G, Asplund K & Olsson T 1999 Leptin is associated with increased risk of myocardial infarction. *Journal of Internal Medicine* **246** 409-418.

Taneli F, Yegane S, Ulman C, Tikiz H, Bilge AR, Ari Z & Uyanik BS 2006 Increased Serum Leptin Concentrations in Patients with Chronic Stable Angina Pectoris and ST-Elevated Myocardial Infarction. *Angiology* **57** 267-272.

Taylor PD, Samuelsson AM & Poston L 2014 Maternal obesity and the developmental programming of hypertension: a role for leptin. *Acta Physiol (Oxf)* **210** 508-523.

Vasseur F, Meyre D & Froguel P 2006 Adiponectin, type 2 diabetes and the metabolic syndrome: lessons from human genetic studies. *Expert Reviews in Molecular Medicine* **8** 1-12.

Vickers MH, Gluckman PD, Coveny AH, Hofman PL, Cutfield WS, Gertler A, Breier BH & Harris M 2005 Neonatal leptin treatment reverses developmental programming. *Endocrinology* **146** 4211-4216.

Vijayakumar M, Fall CH, Osmond C & Barker DJ 1995 Birth weight, weight at one year, and left ventricular mass in adult life. *British Heart Journal* **73** 363-367.

Wallace AM, McMahon AD, Packard CJ, Kelly A, Shepherd J, Gaw A, Sattar N & Committee obotWE 2001 Plasma Leptin and the Risk of Cardiovascular Disease in the West of Scotland Coronary Prevention Study (WOSCOPS). *Circulation* **104** 3052-3056.

Wallerstedt SM, Eriksson AL, Niklason A, Ohlsson C & Hedner T 2004 Serum leptin and myocardial infarction in hypertension. *Blood Press* **13** 243-246.

Yang R & Barouch LA 2007 Leptin signaling and obesity: cardiovascular consequences. *Circ Res* **101** 545-559.

Yzydorczyk C, Li N, Chehade H, Mosig D, Bidho M, Keshavjee B, Armengaud JB, Nardou K, Siddeek B, Benahmed M, et al. 2017 Transient postnatal overfeeding causes liver stress-induced premature senescence in adult mice. *Sci Rep* **7** 12911.

Zohdi V, Lim K, Pearson JT & Black MJ 2014 Developmental programming of cardiovascular disease following intrauterine growth restriction: findings utilising a rat model of maternal protein restriction. . *Nutrients* **7** 119-152.

**LEGENDS TO THE FIGURES**

Figure 1. Means and 95% confidence intervals of the heights and weights of the males and females in the study at each stage of measurement, expressed using WHO standards (https://www.who.int/childgrowth/en/)

Figure 2. Associations between plasma leptin concentration and (A) fat mass and (B) fat percentage, shown separately for men and women.

Figure 3. Mean values (95% confidence intervals) of leptin (A), adiponectin (B) and their ratio (C) at young adult age according to weight at age two years, divided into fifths. Values are adjusted for sex and adult age and weight by regression to the mean values of these variables.