Lifestyle-related diseases have been considered to be caused by genetic factors and lifestyle. In recent years, it has been reported that there is a third factor, based on the developmental origin of health and disease (DOHaD), which involves environmental factors during fetal life and development that are related to health in adulthood and the risk of developing lifestyle-related diseases. In Japan, the percentage of low birth weight (LBW) infants born below 2,500 g has been increasing since around 1980, which seems to correlate with the increase in thinness (body mass index <18.5 kg/m²) of women in their 20s and 30s, inadequate caloric intake during pregnancy, and increasing age at first birth. It is interpreted that infants who acquire a thrifty constitution through this process become relatively overnourished as the nutritional environment improves after birth, leading to an increased risk of developing lifestyle-related diseases. Since it is difficult to correct the acquired frugality after birth, pediatricians need to be aware of the future development of obesity and insulin resistance when monitoring adolescents and young adults born as LBW infants. Physicians caring for adults also need to pay attention to the patient’s birth history, when the patient has a lifestyle-related disease.

**Key words**: low birth weight infant, nonalcoholic fatty liver disease, epigenetics, insulin-resistance, chronic kidney disease

### Introduction

Low birth weight (LBW; defined as infants born weighing < 2500 g) infants are known to be at higher risk of developing non-communicable diseases (NCDs) including lifestyle-related diseases such as diabetes mellitus, hypertension, and hyperlipidemia in adulthood \(^1\) \(^2\). One of the major causes of LBW infants is fetal growth restriction (FGR). FGR refers to a condition in which the fetus does not develop to the equivalent of the length of the pregnancy period, and about 70% of cases are due to placental and maternal factors such as placental insufficiency and maternal diabetes or hypertension. Under these kinds of pathological maternal-fetal environments, exposure to hypotrophic and hypoxic conditions can lead to LBW. In contrast, small for gestational age (SGA) is defined based on the standard values of body size at birth, specifically, described as 'a child whose birth weight and height are less than the 10th percentile of the standard anthropometric values at birth by length of pregnancy'. According to the definition, FGR and SGA are conceptually different, but FGR is often SGA at birth. Another factor in LBW is preterm birth. Preterm infants often receive multidisciplinary care in the neonatal intensive care unit (NICU) during the early postnatal period, resulting in exposure to a low-nutrition environment. Therefore, full-term FGR/SGA and preterm infants have similar
risks of developing lifestyle–related diseases\(^8\).

In the late 1980s, Barker et al. reported an epidemiological cohort study in England and Wales that included more than 15,000 newborns and found that LBW infants appeared to have an increased risk of significantly higher mortality from cardiovascular events (Barker’s hypothesis)\(^1\), following researches determined association with obesity, impaired glucose tolerance, impaired lipid metabolism, and hypertension in adulthood\(^4, 5, 6, 7\). However, Barker’s hypothesis did not adequately account for acquired factors and intergenerational transmis-
sion of disease risk. Later, Gluckman et al. developed Barker’s hypothesis and proposed the Developmental Origin of Health and Disease (DOHaD) theory\(^6\). The DOHaD theory is that environmental factors such as placental insufficiency, maternal overnutrition or undernutrition during fertilization, fetal life, and early postnatal life lead to predictive adaptive responses (PARs), and that a mismatch with the actual postnatal environment is a risk factor for future disease\(^6\).

Recent progress in epigenetic research have led to a better understanding of the molecular biology of the DOHaD hypothesis. Animal studies have suggested that various environmental factors during the developmental period may lead to epigenetic changes, such as DNA methylation and histone modifications, and they may be associated with future health and disease risk\(^6\). In recent years, it has become clear that both underfeeding and overfeeding during the fetal period could be related to the risk for developing metabolic syndrome\(^10, 11, 12\). Meta–analyses from Europe and the United States have shown that the lowest risk of developing metabolic diseases is associated with birth weight of 3.3–4.5 kg, for every 0.5 kg drop in birth weight, the risk of hypertension, diabetes mellitus, and ischemic heart disease increases by about 10\%\(^7\). In this review, we introduce the DOHaD theory by exemplifying specific course of an adolescent born FGR/SGA who presented with obesity, impaired glucose tolerance, abnormal lipid metabolism, and hypertension from school age.

**Lifestyle–related diseases describable by the DOHaD theory: A case presentation**

An 11–year–old Japanese boy visited our hospital with the complaint of proteinuria identified at a regular health check at his school. He was born at the 31\(^{st}\) week of gestational age weighing 880 g \([-5.1\) standard deviation (SD)] due to pregnancy–induced hypertension. His mother was neither obese nor a smoker. Although his mental development was normal, he began to be obese around the age of 4 years, and finally proteinuria appeared at the age of 10 years. His height and weight at the first visit were 150.3 cm and 60.1 kg, respectively, (body mass index (BMI), 26.6 kg/m\(^2\)), and his blood pressure was 128/50 mmHg. Physical examination showed stretch marks and acanthosis nigripens due to obesity. Laboratory analysis [standard value] showed elevated hepatic enzyme levels (alanine aminotransferase (ALT): 185 [6–43] U/L), hyperinsulinemia (insulin 31.5 [2.2–12.4] µU/mL), homeostatic model assessment for insulin resistance (HOMA–IR) 17.7 [<1.6]), hyperglycemia (blood sugar 228 [65–109] mg/dL, HbA1c 10.7 [4.6–6.2] %), dyslipidemia (total cholesterol 202 [<200] mg/dL, high–density lipoprotein cholesterol (HDL–C) 31 [>35] mg/dL, low–density lipoprotein cholesterol (LDL–C) 135 [<130] mg/dL, triglycerides 268 [<150] mg/dL), and hyperuricemia (uric acid 7.7 [3.5–6.9] mg/dL). Urinalysis showed proteinuria (urine total protein/urine creatinine 1.97 [<0.2] g/g Cre; urine albumin/urine creatinine 1.275 [<30] mg/g Cre) and urine sugar (semi–quantitative urine glucose test 1,000 [0–20] mg/dL). Since the absolute liver Hounsfield Unit (HU) value on computed tomography (CT) was 20 to 50, moderate steatosis was expected (Figure 1). Liver and kidney biopsies were performed for further

![Figure 1](image-url)  
(a) Axial unenhanced computed tomography (CT) image. Hepatic attenuation values are 25–50 HU, suggesting that the patient has a fatty liver.  
(b) Visceral fat area measurement by a CT slice at the L4–L5 level. Visceral fat area (blue) 92.7 cm\(^2\); subcutaneous fat area (red) 2538 cm\(^2\); and visceral fat area/subcutaneous fat area ratio 0.37.
evaluation, indicating significant lipid accumulation in both organs and secondary glomerular sclerosis in the kidney (Figure 2). Based on these findings, he was diagnosed with obesity, non-alcoholic steatohepatitis (NASH), diabetes mellitus, and chronic kidney disease. Dietary therapy and medication (metformin, alpha-glucosidase inhibitor, valsartan, and febuxostat) were started immediately after the diagnosis, but insulin therapy was needed two years later because of treatment resistance. The suspected mechanism of the development of metabolic syndrome in this case is shown in Figure 3.

**Japanese Epidemiology and Risk Factors for LBW infants**

Currently, the number of children born with LBW in Japan is increasing, in spite of the decrease in the number of births. According to the population statistics of the Ministry of Health, Labor and Welfare [https://www.mhlw.go.jp/toukei/list/dl/81-1a2.pdf [accessed July 28, 2021] (in Japanese)], the percentage of LBW infants in Japan decreased steadily after World War II, dropping to 5% of around 1975–1980. Since then, the percentage of LBW infants of total births has been increasing, reaching 7% in the 1990s, the same level as in the postwar period, and it has been around 9.5% since 2005. As a result, the current average birth weight of both males and females has decreased by about 200 g compared to the 1975–1980 period.

According to the National Health and Nutrition Examination Survey [https://www.mhlw.go.jp/bunya/kenkou/kenkou_eiyou_chousa.html [accessed July 28, 2021] (in Japanese)], the percentage of women in their 20s who were thin (BMI < 18.5 kg/m²) was 12–15% in the early 1980s, but later started rising, reaching 29.0% in 2010. In recent years, the percentage of women in their 20s who were thin increased significantly, reaching 30.0% in 2010. In recent years, the percentage of women in their 20s who were thin increased significantly, reaching 30.0% in 2010.

**Figure 2** Histological findings of the liver and kidney (a) Liver pathology (hematoxylin–eosin staining x100). A high degree of fat deposition consisting of large and small droplets spread over the whole liver lobule and a small number of centrlobular ballooning hepatocytes are observed. Mild lymphocyte infiltration accompanied by mild fibrosis is also observed, but bridging fibrosis is not seen. Therefore, the pathological stage of NASH is considered to be type 3 according to the Matteoni classification. (b) Kidney pathology (Periodic acid–Schiff staining x400). Glomerular diameter shows hypertrophy (normal range of diameter: 100–150 μm). A glomerulus with increased mesangial matrix, hyaline deposition, and obliterated capillary lumen is observed.

**Figure 3** Relationship between fetal growth restriction and metabolic syndrome

The thrifty phenotype acquired by fetal growth restriction during the maternal–fetal period continues to adversely affect various organs even after birth, increasing the risk of developing lifestyle–related diseases. DM: diabetes mellitus, LBW: low–birth weight infant, FGR: fetal growth restriction, SGA: small for gestational age, NALFD: nonalcoholic fatty liver disease, NASH: nonalcoholic steatohepatitis, CKD: chronic kidney disease.
the percentage has hovered around 20%. This trend is also observed in those in their 30s. The average age of the mother at the time of the birth of her first child was 29.2 years in 2006 and 30.7 years in 2016, an increase of 1.1–1.8 years in all prefectures. Takubo et al. reported in a nutritional survey of 135 normal pregnant women that the average daily energy intake throughout pregnancy was about 1600 kcal, which was 37% less than the recommended value by the Ministry of Health, Labour and Welfare in late pregnancy. The epidemiological background of the increase in LBW infants in Japan has been assumed to be related to thinness in young women, followed by insufficient energy intake during pregnancy and increasing maternal age.

**The Relationship Between LBW and Non-communicable Disease**

1. Epigenetics

Fetuses exposed to a low-nutrient environment in utero becomes FGR to become an LBW infant with restricted growth. At the same time, the fetuses try to adapt to the low-nutrient environment after birth by adopting the situation that is favorable for survival, which is called PAR. This is supposed to be caused by acquired chemical modifications of genome, or epigenetic changes, that regulate the sites of gene expression. Some animal studies suggest that diverse environmental factors during fetal life and development lead to epigenetic changes, such as DNA methylation and histone modifications, that are stored and maintained and involved in future health and disease risk. It is also supposed that FGR sacrifices the development of body size and organs in utero in order to survive in a poor nutritional environment. This abnormal response could become apparent after birth, and this response is called a trade-off. The risk of lifestyle-related diseases in LBW infants is expected to arise on the basis of two responses: PAR and trade-off.

2. Insulin Resistance

Metabolic studies in LBW humans have demonstrated both glucose intolerance and hyperinsulinemia. Morrison et al. reported that extremely low birth weight (ELBW; defined as infants born weighing < 1,000 g) survivors (mean age 32 years) had a 4-fold increased risk of glucose intolerance compared with normal-onset adults. Similarly, Hovi et al. reported that fasting serum insulin levels and the insulin resistance index were significantly higher in adults born as very low birth weight (VLBW; defined as infants born weighing < 1500 g) infants compared to full-term live birth adults. In animal models, some studies reported that insulin-resistance could be associated with impaired pancreatic development, such as decreased pancreatic β-cell mass, β-cell secretory dysfunction, and increased autophagy in β-cells, but the underlying mechanism remains unclear.

3. Nonalcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disease in which fatty liver is present on imaging or histological diagnosis, and other liver diseases such as alcoholic liver disease have been excluded. A meta-analysis in adults estimated the prevalence of NAFLD to be 25.24% worldwide. In Japan, the prevalence rate among adults is 41.0% and 17.7% in males and in females respectively, and 29.7% in total, with increasing trends. In addition, the prevalence of pediatric NAFLD has been reported to be 7.6% in Western countries. According to the data from Japan, the prevalence of NAFLD was 6.6% in boys, 2.0% in girls, and 4.4% overall by ultrasonography screening in elementary and junior high school students. The prevalence of NAFLD among elementary and junior high school students in Japan is estimated to be approximately 4–5%.

Newton et al. reported that children born LBW or high birth weight (HBW) had a significantly higher incidence of NAFLD than the general population of the same age at 13 years (9% vs 6% and 15% and 11%, respectively). Genetic predisposition is also important in the development and progression of NAFLD. Genome-wide association analysis in 2008 showed that hepatic fat content of carriers of the I148M polymorphism of the patatin-like phospholipase domain containing 3 (PNPLA3) gene was more than twice that of non-carriers. In a study evaluating the severity of NAFLD in children, SGA was found to be a factor contributing to severity, as well as PNPLA3 variants. Both over-nutrition and under-nutrition during the fetal period are considered to be high risk factors for developing NAFLD.
4. Chronic Kidney Disease and Hypertension

The development of the human kidney begins around 5 weeks of gestation when the ampulla at the tip of the collecting duct repeatedly branches and elongates, forming a nephron consisting of a glomerulus and a Bowman’s capsule. Nephron formation is completed by 34–36 weeks of gestation, after which no new nephron formation occurs. For infants born at less than 36 weeks of gestation, postnatal nephron formation is suppressed and terminates at about 10–40 days of age. In fact, birth weight and length of gestation are predictors of the nephron number in adulthood. Thus, smaller birth weight and shorter gestational period are associated with a lower number of nephrons in the individual. Based on these studies, Brenner et al. proposed the hyperfiltration theory. In infants with a low number of nephrons, the pressure on the remaining glomeruli is increased, and over-filtration occurs with each nephron. Over-filtration increases intraglomerular pressure and causes compensatory glomerular hypertrophy, leading eventually to nephrosclerosis.

A meta-analysis reported that preterm infants had an average systolic blood pressure 4.2 mmHg higher and diastolic blood pressure 2.6 mmHg higher in adulthood compared with full-term infants. Glucocorticoid overexposure decreases the expression of DNA methyltransferase in the paraventricular nucleus (PVN), one of the blood pressure centers in the fetal brain. This increases the expression of the PVN target gene angiotensin II receptor type 1 (Agtr1a), which causes salt-sensitive hypertension. Thus, the mechanism of hypertension in FGR/SGA children is hypothesized to be secondary to renal dysfunction or due to central epigenetic changes caused by the placental environment.

Clinical Management of LBW Infants

I. Nutritional support

It is difficult to rectify the thrifty phenotype once it has been acquired after birth. Therefore, the parents of LBW infants need to learn proper dietary habits to prevent obesity and insulin resistance in the future. Guidance from the American Academy of Pediatrics recommends the following to avoid future obesity from infancy: (1) continued breastfeeding until 6 months of age; (2) no weaning before 4 months of age; (3) no fruit juices or juice containing fructose or sucrose; (4) supine position when awake to increase activity; and (5) no smoking by the mother. The same kind of nutritional management is required in children and young adults born LBW.

2. Short stature due to SGA

It is known that children born with SGA who do not have a catch-up by the age of 2 years will have short stature throughout childhood, which is called small-for-gestational-age short stature. A study of the natural history of 3,650 children with SGA reported that the percentage of cases with a height standard deviation score (SDS) below -2 SD at each age was 13.7% at age 2 years, 8.3% at age 5 years, and 7.9% at age 18 years. Height growth is not expected after age 5 years. The efficacy and safety of growth hormone (GH) therapy for children with SGA-induced short stature have been examined. In Japan, GH treatment is available within the insurance system for children with SGA-induced short stature who are 3 years of age or older, have a height SDS of less than -2.5, and are experiencing a decreased rate of height gain.

3. Monitoring for the Future Development of CKD and Hypertension

How to follow-up on LBW infants, which now account for about 9% of all births, is an important issue. Infants born with FGR and those with kidney dysfunction or late-onset circulatory collapse on admission to neonatal intensive care units are at high risk of developing CKD. Forty-five years have passed since the screening of renal diseases by school urinalysis started in Japan. Recently, some reports showed that glomerulosclerosis (FSGS) patients born with FGR were diagnosed as a result of regular screening tests at their school. It is also known that tubular dysfunction commonly occurs in ELBW survivors. It is difficult to detect trace amounts of protein in urine with the qualitative test (test paper method) used in the routine health check. Therefore, blood pressure measurement, the urinary N-acetyl-β-D-glucosaminidase-to-creatinine ratio (NAG/Cr), and the β2 microglobulin-to-creatinine ratio (β2m/Cr) are useful in regular follow-up visits to detect early renal complications.
Renin-angiotensin system (RAS) inhibitors such as angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are recommended as first-line antihypertensive therapy for CKD patients with urinary protein, with or without diabetes mellitus (https://www.jpnsh.jp/data/jsh2019/JSH2019_hp.pdf [accessed July 28, 2021] in Japanese). In ELBW survivors with glomerular hypertension, RAS inhibitors may also have similar efficiency. Long-term follow-up of these patients would be needed even in adulthood.

Conclusions

The mechanism of the development of lifestyle–related diseases in FGR/SGA infants was introduced from the perspective of the DOHaD theory in this review. According to Japanese population statistics, in 2025, about 10% of people aged 20 years are predicted to have a birth history of LBW, and the trend will continue. This trend is unique to Japan, so that Western European countries are interested in the epidemiological trends of lifestyle–related diseases in Japan in the near future. Therefore, it is important for obstetricians to educate and support pregnant women with respect to their eating habits. In addition, pediatricians need to teach parents of FGR/SGA infants about dietary habits to prevent the future risk of obesity and insulin resistance in their offspring. Furthermore, physicians caring for adults should keep in mind the new third factor of lifestyle–related diseases based on the DOHaD theory by checking the birth history in daily practice.

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Author contributions

MS participated in writing the manuscript and creating the figures. SN carried out clinical assessments of the patient and performed the histological examination of the liver and kidney, and YM and KM revised the manuscript for intellectual content. All authors read and approved the final manuscript.

Declaration of conflicting interests

All the authors of this study declare that they have nothing to disclose regarding funding or conflict of interest with respect to this manuscript.

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