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Low birth weight: impact on women's health

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Abstract

Purpose—First proposed by Dr. David Barker and now supported by numerous epidemiological and experimental studies, the theory of the developmental origins of health and disease hypothesizes that low birth weight (5.5 pounds or less) indicative of poor fetal growth is associated with an increased risk for chronic, non-communicable disease in later life including hypertension, type 2 diabetes and osteoporosis. Whether women are at greater risk than men is not clear. Experimental studies that mimic the cause of slow fetal growth are being used to examine the underlying mechanisms that link a poor fetal environment with later chronic disease and investigate how sex and age impact programmed risk. Thus, the aim of this review is to summarize the current literature related to the impact of low birth weight on women's health and provide insight into potential mechanisms that program increased risk of chronic disease across the lifespan.

Methods—A search of PubMed was utilized with key words related to low birth weight, women's health, female and sex differences; additional terms included blood pressure, hypertension, renal, cardiovascular, obesity, glucose intolerance, type 2 diabetes, osteoporosis, bone health, reproductive senescence, menopause and aging.

Findings—The major chronic diseases associated with low birth weight include high blood pressure and cardiovascular disease, impaired glucose homeostasis and Type 2 Diabetes, impaired bone mass and osteoporosis, and early reproductive aging.

Implications—Low birth weight increases the risk for chronic disease in men and women. Low birth weight is also associated with increased risk for early menopause. Further studies are needed to fully address the impact of sex and age on the developmental programming of adult health and disease in women across their lifespan.

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CONFLICT OF INTEREST
The authors have no conflicts of interest.

Keywords

low birth weight; women's health; blood pressure; type 2 diabetes; osteoporosis; early menopause

INTRODUCTION

The theory of the developmental origins of adult health and disease (**DOHaD**) was first proposed by David Barker and colleagues who noted a geographical association between deaths from coronary heart disease and infant mortality (6). Low birth weight indicative of slow growth during fetal life contributes to infant mortality and morbidity. Thus, they proposed that events during fetal life that slow fetal growth may increase cardiovascular (**CV**) risk in individuals that survive a complicated pregnancy (7). To further their investigation Barker examined the association between high blood pressure, a risk factor for CV disease, and low birth weight (**LBW**), a marker of poor fetal growth, and noted an inverse relationship between birth weight and blood pressure supporting their original hypothesis (5). Since these initial observations numerous epidemiological studies have investigated the inverse association between birth weight and blood pressure (for systematic review see 50) and substantiated Barker and colleagues findings. Furthermore, additional studies indicate that birth weight is inversely associated with an increased risk for Type 2 Diabetes (T2D) (64, 99) and osteoporosis (58) (Figure); LBW also increases the risk for early menopause (19, 86, 95) (Figure). Experimental models are providing proof of principle and use of experimental models that mimic the pathophysiological and environmental conditions that slow fetal growth are being use to investigate the underlying mechanisms that link fetal life and chronic disease in later life (8, 17,36, 41, 108) (Figure). Thus, the goal of this review is to highlight the current field and explore how LBW and influences that slow growth during fetal life impair chronic health and disease in women.

METHODS

An electronic search was conducted via PubMed related to the impact of low birth weight on chronic health in women and in experimental models of developmental programming of CV disease, T2D, and osteoporosis.

RESULTS

Low birth weight and experimental models of developmental programming

LBW results from a number of different factors including maternal complications such as preeclampsia or diabetes, improper nutrition, poor prenatal care, maternal smoking and age (48, 105). Teenagers and women over 40 are at greater risk for a LBW baby (63). Race also impacts the risk of low birth weight with African American woman having a two-fold increased risk compared to American women of European descent (63). Maternal smoking also increases the risk for a LBW baby by two-fold (90) and maternal infection, placental abruption are also causative factors (48). Numerous studies now indicate that complications during pregnancy increase the risk for chronic disease in later life of the offspring (1, 12,23, 84, 98). Preeclampsia is associated with an increased risk of LBW and the development of

hypertension and CV complications in the offspring (23, 84). Children born to pregnancies complicated by diabetes also demonstrate an increased risk for hypertension, CV disease (1, 98) and metabolic disturbances including T2D (12). Experimental models that mimic the etiology of LBW are being used to explore the underlying mechanisms that link a poor fetal environment with later increased chronic disease. Poor fetal nutrition is associated with hypertension in later life (85) and undernutrition during fetal life induced via protein restriction in the rat is a commonly used model to study the mechanisms that program hypertension (103) or impaired glucose homeostasis (72) in the offspring after birth. The initiating event in preeclampsia involves placental insufficiency (35). Placental insufficiency in the rat is another model used to study the developmental programming of hypertension (3) and glucose intolerance (44, 88) in the intrauterine growth restriction (**IUGR**) offspring. Fetal exposure to maternal glucocorticoids impairs fetal growth (73) and expression of placental 11beta-hydroxysteroid dehydrogenase type 2 (**11beta-HSD2**), the enzyme that protects the fetus from exposure to maternal glucocorticoids (73), is reduced in pregnancies complicated by preeclampsia (81). Experimental models of fetal exposure to glucocorticoid are being utilized to elucidate the renal mechanism that program hypertension following a developmental insult (71). Prenatal exposure to nicotine is used to mimic the adverse impact of maternal smoking during pregnancy (105). Thus, this model of prenatal insult is being used to mimic the causative factors that impair growth during prenatal life and program increased risk for chronic disease (77). These different models of developmental insults are providing insight into the mechanisms that link complications during pregnancy or impaired fetal growth with later chronic disease. They also demonstrate that the fetal responses to a developmental insult are sex-specific and result in sex-specific outcomes on chronic health. This review will discuss the impact of LBW on chronic health and disease and provide insight into known mechanisms with a special emphasis on women's health.

Low birth weight and blood pressure: increased cardiovascular risk

Birth weight is inversely related to blood pressure in men (21) and women (20). Age greatly impacts the risk of high blood pressure in LBW women (5) and accelerated weight gain in early life adds to the risk (51). It is well established that within the general population men have a higher blood pressure than women prior to menopause although age abolishes this difference (54). Differences in CV risk factors may contribute to this sex difference in blood pressure in men and women in young adulthood (47). Being born small for gestational age (**SGA**) is associated with higher LDL and lower HDL cholesterol levels in young adulthood relative to appropriate for gestational age (**AGA**) counterparts (79). Yet, prenatal undernutrition is associated with an increase in total cholesterol concentration in women at 58 years of age but not men (55). Whether LBW programs sex-specific differences in CV risk that is age-dependent is not yet reported. However, birth weight is inversely associated with coronary heart disease in men (30) and in women after menopause (52, 107). Vos et al. examined the relationship between size at birth and the absolute 10-year CV risk in young adulthood (96). They reported that small size at birth increased overall CV risk in men and women; however, CV risk was greater in LBW men relative to LBW women (96). Thus, birth weight is inversely associated with blood pressure and risk for coronary heart disease in women. However, risk is greater in LBW men relative to LBW women prior to

menopause; age may impact this risk and the mechanisms that mediate the sex difference in programmed risk require further investigation.

Numerous experimental studies note a sex difference in blood pressure in offspring exposed to insults during early life (3, 62,71,101, 103,104, 105). Blood pressure is significantly elevated in male offspring exposed to placental insufficiency (3, 101), maternal protein restriction (103), or prenatal exposure to glucocorticoids (71); yet female offspring in these models of developmental insult do not develop hypertension in young adulthood (3, 62, 104). Extensive investigation has centered on the role of the renin angiotensin system (**RAS**) in the etiology of hypertension programmed by *in utero* insults. The RAS contributes to the long-term control of blood pressure through its influence on sodium reabsorption, aldosterone secretion and vasoconstriction. Inhibition of the RAS abolishes hypertension in male offspring exposed to prenatal protein restriction (56) and placental insufficiency (69) implicating an important role for the RAS in the etiology of hypertension programmed by a developmental insult. Circulating levels of angiotensin II (**Ang II**) and ACE activity are elevated in SGA boys but not SGA girls (32) providing support for inappropriate activation of the RAS within a human cohort and a potential mediator of increased CV risk observed in boys relative to girls following a developmental insult. In the experimental rat model of placental insufficiency expression of renal ACE2, a component of the vasodilator arm of the RAS is elevated in female IUGR rats that are normotensive in adulthood (68). Thus, up-regulation of vasoconstrictor arm of the RAS may contribute to the development of increased CV risk in males exposed to a developmental insult whereas up-regulation of the vasodilator arm may be a compensatory mechanism that protects against programmed CV risk in the young female. Oxidative stress is a known contributor to hypertension and CV disease (99). Markers of oxidative stress are elevated in children born SGA (33) and in male rats exposed to maternal protein restriction (87) or placental insufficiency (70). Antioxidants abolish hypertension in these male offspring; yet, female IUGR offspring exposed to placental insufficiency that are normotensive in young adulthood do not exhibit an increase in renal markers of oxidative stress (70). Renal antioxidant expression and activity are up-regulated in the female IUGR rats that are normotensive in young adulthood in this model implicating a compensatory mechanism that may be protective against the generation of reactive oxygen species in the young female IUGR rat. Thus, experimental models suggest that sex specific programming of the RAS and oxidative stress contribute to the sexual dimorphism of blood pressure in experimental models of fetal insult and implicate the RAS and oxidative stress as potential mediators of increased risk in LBW individuals.

Blood pressure increases with age within the general population (54). Recent studies indicate that age may also increase CV risk in female offspring exposed to a developmental insult. Female IUGR offspring in a model of placental insufficiency are normotensive in early adulthood relative to their same-sex control counterparts (3). Yet, a marked increase in blood pressure is observed by 12 months of age relative to control (42) indicating that age serving as a second hit increases CV risk following IUGR in the female rat. Increases in total fat mass and visceral adiposity are noted in conjunction with the age-dependent increase in blood pressure in female IUGR induced via placental insufficiency (42). Whether the increase in adiposity directly contributes to the development of age-dependent

hypertension in this model is not clear. However, the increase in adiposity in the female IUGR rats at 12 months of age is associated with an increase in circulating levels of leptin, an adipokine released from adipose tissue (42). Leptin contributes to the development of obesity-related hypertension via activation of the renal sympathetic nerves (38). Renal denervation abolishes age-dependent hypertension in the female IUGR rats at 12 months of age (42) implicating an important role for the renal nerves. The renal nerves also contribute to hypertension in male offspring in young adulthood programmed by fetal exposure to placental insufficiency (4) or glucocorticoids (22) implicating similar pathways contribute to programming of hypertension following a developmental insult but in a manner that is age-dependent. Age also impacts the development of increased CV in offspring exposed to prenatal nicotine (105). Overt hypertension is not observed in all models of developmental insult (105). Male and female offspring exposed to prenatal nicotine are normotensive in young adulthood but male offspring exhibit an enhanced sensitivity to vasoactive factors such as Ang II, a marker of increased CV risk (105). Yet, sensitivity to Ang II is not enhanced in female rats exposed to prenatal nicotine until 22 months of age (91). Thus, these studies indicate that age abolishes protection against the developmental programming of CV risk observed in young female animals and highlights the need for additional studies to determine the sex- and age-dependent mechanisms that programming hypertension and increased CV risk in LBW women.

Low birth weight and adiposity and glucose homeostasis: risk for Type 2 Diabetes

A systematic review of the literature conducted in 2003 noted an inverse relationship between birth weight and several glycemic indices including fasting plasma glucose, fasting plasma insulin and two-hour glucose that is present in men and women (64) suggesting that influences that slow growth during fetal life program impaired glucose homeostasis in later life. The inverse relationship between birth weight and the risk for development of T2D is noted in men (15, 99) and women (24, 74, 99). However, findings from the Australian Diabetes, Obesity and Lifestyle (AUSDIAB) Study report that the association between birth weight and an increased risk for T2D is greater in LBW women relative to LBW men, an association that is present independent of current body mass index (BMI) (2). In this study high fasting plasma glucose and high mean hemoglobin A1c were strongly and inversely associated with birth weight with the proportion for all glycemic abnormalities greater in LBW women relative to LBW men (2). Mogren et al. observed an elevation in fasting plasma glucose and two-hour plasma glucose in LBW women relative to their normal birth weight counterparts that was only noted in LBW men in conjunction with a hereditary background for T2D (67). Both of these studies used cohorts composed of young adults, average age 25 and 32, respectively (1, 67). Studies that examine this association at older ages report that an increased risk for T2D is present in LBW women by 50 years of age (24) with the risk for T2D increased after menopause in African American women (76). LBW is also associated with an increased risk of central visceral adiposity (20) with females more susceptible relative to males (106). LBW when coupled with accelerated weight gain in childhood regardless of sex also increases the risk for the metabolic syndrome in young adulthood (65). Women with LBW are also at increased risk for glucose intolerance during a first pregnancy (91) and the development of gestational diabetes mellitus (**GDM**) (10, 39, 67). GDM is a strong predictor of later T2D (18). Thus, LBW indicative of poor fetal

nutrition and slow growth during fetal life increases the risk for impaired metabolic health during pregnancy and in later life in LBW women and indicates that susceptibility to diabetes is programmed during early development.

Experimental studies are providing insight into the mechanisms that program impaired metabolic health and also highlight that exposure to adverse events during early life program impaired glucose homeostasis in a manner that is sex, age and insult specific. Insulin release in response to a glucose challenge is impaired in both male and female offspring of protein restricted dams but only male offspring exhibit a reduction in beta-cell mass (94) and insulin resistance in young adulthood (89). Yet, placental insufficiency programs a reduction in beta cell mass in male and female IUGR offspring at 3 months of age that is not associated with impaired glucose tolerance but is associated with lower glucose-stimulated insulin release in the female IUGR rats relative to female control (88). Placental insufficiency also programs an increase in mean fasting glucose levels in female but not male IUGR offspring at this age (44). Fasting glucose levels do not differ in either sex by 6 months of age following fetal exposure to placental insufficiency but glucose intolerance is observed in male IUGR offspring (82). Maternal protein restriction programs an increase in fasting glucose levels in male offspring that is associated with glucose intolerance by 21 months of age (72). Although maternal protein restriction is not associated with changes in fasting glucose or glucose intolerance in female offspring at this age (31), fetal exposure to maternal protein restriction programs hyperinsulinemia associated with a reduction in insulin-signaling protein expression in the female offspring by 21 months of age (31). Glucose tolerance is impaired in female IUGR offspring during their pregnancy indicating that pregnancy increases vulnerability to metabolic disturbances following a developmental insult (34). Additionally, hyperglycemia, hyperinsulinemia, and unsuppressed hepatic glucose production are observed in offspring of female rats exposed to nutrient restriction during their gestational life implicating that programming of impaired metabolic health is transmitted to the next generation (93). Thus, further studies are needed to clearly elucidate the impact that poor nutrition and growth during fetal life have on later metabolic health and to determine the exact mechanisms that underlie the sex specific developmental programming of T2D in later life and in response to a physiological challenge such as pregnancy.

Low birth weight and bone health: risk for osteoporosis

Osteoporosis is the most common bone disease. It involves compromised bone strength and results from an imbalance in bone formation and bone reabsorption leading to an increased risk for bone fracture (9). Menopause is associated with an increase in osteoporosis due to changes in bone remodeling mediated by estrogen deficiency (92). Smoking, excessive alcohol and caffeine intake, inadequate calcium/vitamin D intake and lack of weight bearing exercise are all modifiable risk factors for osteoporosis (92). Other factors such as sex and genetics also impact bone health with older women exhibiting a higher prevalence of bone fracture relative to age-matched men (16). A recent systematic review and meta-analysis of the literature noted that birth weight is associated with bone health in childhood implicating that bone density has its origins during fetal life (58). Yet, the impact of birth weight on bone health during adolescence and adulthood is not clear. A systematic review of the

literature suggests that low birth weight is associated with low adult bone mass with the association for low birth weight greater for bone mineral content than for bone mineral density, or the ratio of bone mineral content to bone size (80). Yet, individual studies indicate contradictory findings. Jones et al. report that low birth weight is associated with a reduction in bone mass, an indirect marker of fracture risk, at 8 (45) but not at 16 years of age (46) in boys and girls. However, El Hage et al. report that low birth weight is associated with low bone mineral content and bone mineral density in girls at 15 years (27). Callreus et al. note that low birth weight is associated with low bone mineral content in women at 25 years of age (14) and Yarbrough et al. report that low birth weight remains associated with low bone mineral content in women at 70 years of age (107). Dennison and colleagues report that birth weight is a determinant of bone strength in men and women at 70 years of age (26). Yet, Byberg and colleagues report that despite a positive association between birth weight and bone mineral content, low birth weight is not associated with an increased risk of fracture in men and women aged 50–94 years (13).

Experimental studies also differ in regards to the importance of fetal life on later bone health. Lanham et al reported that rat offspring of protein restricted dams exhibit a reduction in bone density and mechanical strength in female offspring (49). Placental insufficiency in the rat also programs a reduction in bone mineral content and bone strength in the offspring with lower bone density noted in the female growth restricted offspring relative to male (78). Additionally, findings from this study noted that supplementation with calcium starting in adolescence does not reverse the bone strength deficient initiated by placental insufficiency in the growth-restricted offspring (77) suggesting that developmental influences that impair bone health are not reversible with post-natal interventions. Engelbregt et al. observed that a reduction in bone mineral content in male and female offspring exposed to prenatal malnutrition or placental insufficiency does not remain significant at 6 months of age after adjustment for total body weight (29); yet Metha et al. reported that a reduction in bone mass occurred with age in offspring exposed to protein restriction during fetal life (60). Therefore, numerous epidemiological and experimental studies indicate that risk of osteoporosis may have its origins in fetal life. Studies thus far indicate that females may be more susceptible to risk for osteoporosis following an insult during fetal life than males. However, the impact of age and transition into menopause on bone health in low birth weight women has not yet been explored and further studies are needed to determine the mechanistic pathways that link fetal life with later bone health in order to develop preventative and therapeutic options.

Low birth weight and menopause: risk for early reproductive senescence

Menopause usually occurs around 52 years of age and indicates the end of reproductive viability (11). Risk factors for early onset menopause include smoking, stress within the African American population, nulliparity, and genetics (11). Early menopause is positively associated with coronary heart disease and stroke independent of other cardiovascular risk factors (97). Recent studies indicate that LBW may be a risk factor for earlier age at menopause (19, 86, 95) and women exposed to famine during late gestation exhibit a greater prevalence of early onset menopause (28, 108). Experimental studies indicate that prenatal exposure to undernutrition in the rat is also associated with markers of early reproductive

senescence (8, 36, 17) as indicated by a reduction in ovarian follicle numbers (8, 17) and early onset of estrous acyclicity following maternal undernutrition (17). Thus, LBW indicative of undernutrition and slow growth during fetal life programs early onset reproductive senescence suggesting that accelerated reproductive aging may contribute to the increased risk of chronic diseases such as CV, metabolic, and osteoporosis in LBW women.

Low birth weight and gestation: risk for complications during pregnancy

LBW increases a woman's risk for complications during pregnancy including hypertension (25, 40), GDM (38) and birth of a LBW baby. Preeclampsia is a disorder associated with significant endothelial dysfunction (59). LBW is also associated with endothelial dysfunction with observations noted in children (57) and young adults (53). Therefore, LBW may program an increased risk for hypertensive complications during pregnancy due to the increase in preexisting cardiovascular risk factors. LBW also increases the risk for GDM (39). Furthermore, complications during pregnancy including the birth of a LBW baby increase the mother's risk of later T2D (43) and CV disease (75) in her life. Thus, complications during pregnancy in one generation resulting in impaired fetal growth can impact the gestational health of the next generation. These studies indicate that influences during fetal life have long reaching impact on subsequent generations. The exact mechanisms are not known but epigenetic processes are thought to contribute to the transmission of programmed risk from one generation to the next (66) and could conceivably contribute to the risk for a complicated pregnancy in a LBW woman. Thus, LBW as a consequence of a complicated pregnancy increases a women's own risk to have a complicated pregnancy and also increases her risk for chronic disease in later life. Complicated pregnancies also program an increased CV and metabolic risk in the offspring highlighting the broad impact and severity that slow fetal growth in one generation has on the quality of life and health of the next.

CONCLUSIONS

Slow growth during fetal life exerts an adverse influence on gestational and chronic health in women. Low birth weight indicative of poor fetal growth increases the risk of early onset menopause, cardiovascular and metabolic disease, and osteoporosis in later life. Experimental models are providing insight into the underlying mechanisms that program later increased risk for chronic disease in women. Yet, additional studies are needed to provide insight into preventative and therapeutic options that may intervene and reduce the risk of chronic disease in low birth weight women across their lifespan and improve their gestational health to prevent the transmission of programmed risk to the next generation.

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HIGHLIGHTS

- Low birth weight programs an increased risk for chronic disease in men and women. However, women may differ in their susceptibility to chronic disease risk relative to men in a manner that may be impacted by age.
- Low birth weight is associated with early menopause. Early menopause is a risk factor for cardiovascular and metabolic health. Early menopause can also impact bone density suggesting that early reproductive senescence programmed in response to slow growth during fetal life may exacerbate risk for chronic disease that is already inherent in low birth weight women.
- Low birth weight increases a woman's risk for complications during pregnancy. Thus, the impact of poor fetal growth in one generation impacts the chronic health of subsequent and future generations highlighting the importance of understanding how slow growth during fetal life impacts a women's health across her lifespan.

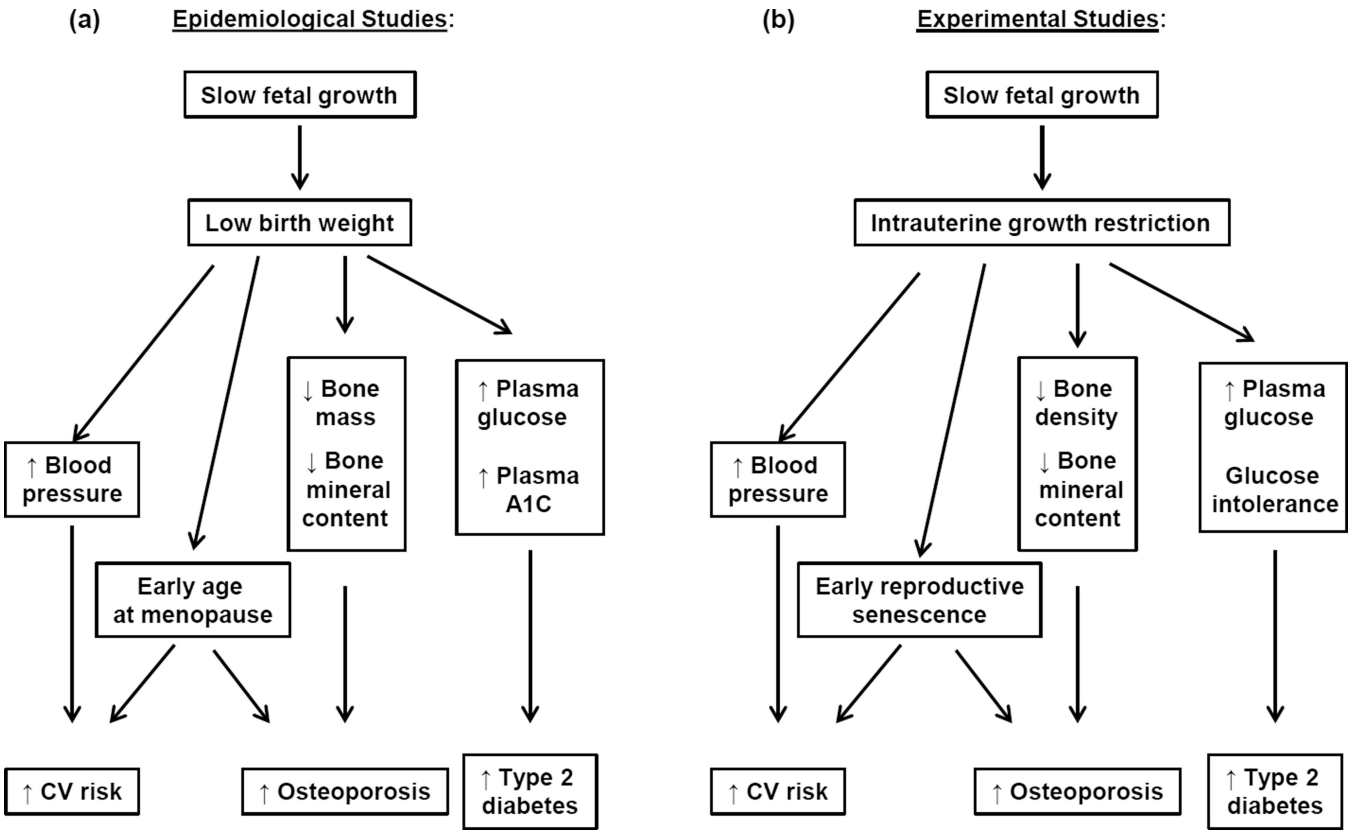

Figure 1.

Epidemiological studies indicate that slow growth during fetal life programs an increased risk for cardiovascular (CV) disease, Type 2 Diabetes, osteoporosis, and earlier age at menopause in low birth weight women (A). Experimental models that mimic slow fetal growth are providing proof of concept (B) and are also allowing investigation in the mechanisms that link low birth weight with later chronic disease in women.