ASSOCIATION BETWEEN INFANT BIRTH WEIGHT, PRETERM DELIVERY AND MATERNAL CARDIOVASCULAR RISK IN THE HEALTH, AGING AND BODY COMPOSITION STUDY

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Mothers who deliver a low birth weight infant may themselves be at excess risk for cardiovascular disease. We validated maternal recall of infant birth weight after an average follow up of 57 years, and investigated whether older women who reported having delivered low birth weight (LBW) infants (<2500 g) had later elevations in cardiovascular risk factors and were at increased risk for clinical cardiovascular disease. Participants were 446 women (mean age 80 years; 47% black) enrolled in The Health, Aging and Body Composition Study. Women reported birth weight and selected complications for each pregnancy, and pregnancies complicated by hypertension or preeclampsia were excluded. We found strong correlation between recalled and documented birth weights for first births (ICC=0.96) in a randomly selected group of participants, and reliability of recall for first births remained high when considered separately by race, education, income and age. Women who had reported a LBW first birth had a lower current BMI (adjusted for race and age) compared to women with normal weight infants (26.6 vs. 28.0 kg/m²; p=0.057), but they had a higher abdominal circumference (98.1 vs. 95.0 cm; p=0.007). After adjustment for BMI, race and age, women with a history of a LBW vs. normal weight infant had elevated systolic blood pressures (p=0.048) despite higher use of anti-hypertensive medication (p=0.061). Women with LBW infants also had higher levels of IL-6 (p=0.021), fasting insulin (p=0.064), and triglycerides (p=0.071), and they were more

insulin resistant (p=0.045) compared to women with a normal weight infant. Women who delivered preterm infants had an elevated risk for cardiovascular disease at age 80 (adjusted odds ratio=2.77, 95% CI 1.06-7.24) compared to women who delivered term infants. Women who had delivered infants both LBW and preterm had markedly elevated cardiovascular risk factors when compared to women with normal weight term infants, and appeared to have the highest risk for clinical cardiovascular disease (adjusted odds ratio=4.21, 95% CI 1.23-14.45). The public health importance of these findings is that a history of LBW or preterm delivery may identify women who would benefit from screening and intervention aimed at risk factors for cardiovascular disease.

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DEDICATION

I dedicate this project to my parents, Betty and Peter Catov, who died too young to see how far their daughter's education took her. I also dedicate it to my aunt, Margaret Trotter, who instilled in me a no-nonsense work ethic and provided a role model for the committed, bright and successful woman I had hoped to become.

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1. INTRODUCTION

1.1. SPECIFIC AIMS

Emerging evidence suggests that mothers who deliver a growth restricted or preterm infant may themselves be at excess cardiovascular risk. Two large observational studies have found that low birth weight (<2500 g.) delivery may increase risk for cardiovascular disease seven to 11-fold. [1, 2] In addition, two studies found that risk for cardiovascular death was twice that for women with a history of preterm delivery compared to those who had delivered at term. [3, 4]

The study of cardiovascular disease in women has focused typically on traditional risk factors that women share with men. Women, however, experience gender specific exposures that may affect cardiovascular risk, such as pregnancy. The Health, Aging, and Body Composition (Health ABC) Study is a large on-going epidemiologic study of how changes in body composition affect morbidity, disability and risk of mortality. This cohort is ideally suited to study the association between pregnancy history and maternal cardiovascular risk as there are extensive outcome data already collected, participants continue to be contacted annually, and they are racially diverse.

Pregnancy history data are limited in the main Health ABC study, so this study will collect these data retrospectively through participant interview. We hypothesize that delivery of a small or preterm infant will act as a marker of women at increased risk for cardiovascular

disease. In addition, we hypothesize that a poor pregnancy outcome of low birth weight or preterm delivery will interact with other risk factors across a woman's lifetime to elevate her future risk for cardiovascular disease.

It is important to test these hypotheses in a group of women with detailed clinical cardiovascular risk data to determine if the association is spurious or real. If an association exists between infant birth weight and future cardiovascular disease, this may provide an early marker of women who should be targeted for interventions long before clinical manifestation of disease. In addition, understanding how maternal chronic disease risks might be involved in mechanisms leading to low birth weight or preterm delivery could provide important insight into these persistent public health challenges.

This is a cross-sectional study designed to examine the association between delivery of a low birth weight (< 2500 g) infant and cardiovascular morbidity to achieve the following scientific objectives:

1. To assess whether women who have born a low birth weight infant have later elevations in blood pressure, lipid profiles, glucose concentrations, IL-6, CRP and pulse wave velocity.
2. To determine if women who delivered a low birth weight or preterm infant have an increased risk of coronary artery disease, stroke or peripheral vascular disease compared with women who delivered a normal weight infant.
3. To determine how birth outcomes might interact with other risk factors over the course of a woman's lifetime, such as obesity, race and smoking, to mediate risk for cardiovascular disease.

1.2. BACKGROUND AND SIGNIFICANCE

1.2.1. Epidemiology of low birth weight and preterm delivery

Low birth weight (LBW) has been considered the most important newborn characteristic predicting infant mortality. [5-7] LBW has also been associated with long term morbidity in children, including mental retardation, cerebral palsy, sensory perception, school performance, and overall quality of life. [8] In addition, delivery of one LBW or preterm infant is the single strongest predictor of subsequent LBW or preterm delivery. [9]

Low birth weight newborns are defined by the World Health Organization (WHO) as those weighing less than 2500 g. at birth. LBW and preterm delivery (before 37 weeks gestation) are intimately related; 60% of LBW births were also preterm. [10] LBW can also result from intrauterine growth restriction (IUGR) in infants born at or near term. IUGR refers to a biological phenomenon of restricted growth relative to the genetic potential of an infant. Small for gestational age (SGA) is a statistical phenomenon typically categorized as infants at the bottom 10^{th} percentile for weight for a given gestational age, [11] and is often used as a proxy for IUGR. It is estimated that 4 to 8% of all infants are growth restricted, and 25 to 33% of LBW infants have sustained IUGR. [12] IUGR and/or preterm infants can be classified in the following categories: [12]

Table 1: Classification of Preterm and Growth Restricted Infants

Category	Definition
Preterm neonates	Newborns delivered before 37 completed weeks gestation who are of appropriate size for gestational age
Preterm and growth-restricted	Newborns delivered before 37 completed weeks gestation who are small for gestational age
Term growth-restricted	Newborns delivered after 37 completed weeks gestation who are small for gestational age

Classifying newborns in this way, however, requires an accurate birth weight as well as an accurate determination of gestational age. Gestational age determination requires a combination of antepartum ultrasound results and date of last menstrual period, and these clinical data are not always available. Epidemiologic studies must at times rely on birth weight as a marker for prematurity or growth restriction because accurate gestational age data may not be available.

The rate of low birth weight resulting from both IUGR and/or preterm delivery in the U.S. has gone from 7.9% in 1970 to 6.8% in 1980 to 7.7% in 2001. [13] Rates are increasing for white women, but rates for black women continue to be more than double those of whites. The rate of preterm delivery is higher than LBW and on the increase; preterm delivery rates were 9.8% in 1985 and 12.1% in 2002. [14] Infants born both preterm and LBW are at greatest risk for morbidity, mortality and disabilities. [10]

Causes of preterm delivery are mutifactorial, with about 40% of cases due to premature spontaneous labor, 40% due to premature rupture of membranes, and 20% due to fetal or maternal indication. [8] The mechanisms that lead to preterm delivery or LBW are thought to fall into several different pathologic pathways that involve both endogenous and exogenous exposures. [12] The following chart summarizes the action along these possible pathways, and is adapted from Mattison, et al. [10]

Table 2: Pathways to iatrogenic preterm and/or low birth weight delivery

Pathway	Possible Mechanism
Familial aggregation	The single largest risk factor for preterm delivery is previous preterm delivery. Family studies have demonstrated increased risk of preterm delivery and LBW among siblings.
Maternal stress	Acute or chronic maternal stress has been suggested as increasing risk for preterm delivery. Thought to operate through maternal, placental and fetal hormonal mechanisms.
Fetal stress	Fetal stress due to inadequate nutrition, oxygenation, or infection may produce hormones signally the onset of labor. Preterm delivery for these reasons may also be medically induced, such as with preeclampsia
Bleeding	Bleeding into the myometrium of the uterus acts as a stimulant to contractions.
Inflammation	Initiation of inflammatory responses with release of maternal or fetal cytokines, interleukins or molecular modulators of inflammation may initiate uterine activity.
Fetal infection	Fetal infection is a stressor that appears to initiate uterine activity.
Maternal infection	Infection of the uterus, placenta or systemic infection.
Mechanical	Abnormally small uterine cavity, multiple gestation or abnormal or incompetent cervix.

It is possible that genotypes and phenotypes implicated in the risk for LBW or preterm delivery may also play a role in maternal vascular disease. Underlying risk for cardiovascular disease may affect a woman's ability to successfully adapt to the vascular or metabolic demands of pregnancy, leading to poor pregnancy outcomes during the reproductive years and higher cardiovascular risk later in life. [15] In particular, family aggregation, inflammation and infection may be pathways linking these health outcomes.

1.2.1.1. Familial aggregation

There has been strong evidence that the composite endpoint of low birth weight, resulting from IUGR or preterm delivery, aggregates in families. Wang, et al completed one large study that found adjusted odds of a woman delivering LBW after an earlier LBW pregnancy was 6.8 (95% CI 4.7 to 9.8) for whites and 4.7 (95% CI 3.5 to 6.4) for blacks. [16] The odds of delivering a LBW infant more than doubled when the mother herself was LBW and she had a previous LBW pregnancy. Utilizing data from the Collaborative Perinatal Project, Klebanoff, et al found that infants born to mothers who themselves were LBW were on average 244 g. lighter than infants of mothers who weighed 8 pounds or more at birth. [6] Odds of delivering a LBW infant when the mother herself was born LBW were 3.46 (95% CI 1.5 to 7.9) compared to the reference group of mothers who weighed 8 pounds or more at birth.

Reduced placental perfusion, implicated in both IUGR [17] and preterm birth [18], could involve both genetic and environmental components that cause these poor pregnancy outcomes to aggregate in families. Roberts and Cooper have suggested a maternal genetic contribution to the incomplete remodeling of the spiral arteries resulting in restricted placental perfusion [19], and environmental influences such as cigarette smoking could also restrict adequate blood flow to the placenta. [20]

1.2.1.2. Infection and inflammation

Infection and inflammation have also been strongly associated with preterm delivery, especially very early preterm births occurring before 33 weeks completed gestation. In women with spontaneous preterm labor and intact membranes the most common vaginal organisms are of relatively low virulence. [21] It appears that these bacteria ascend into the uterus, perhaps even prior to pregnancy, and some women may sustain chronic intrauterine infections between

pregnancies which could cause repeated spontaneous preterm deliveries. [22] Goldenberg, et al found in the Preterm Prediction Study that risk for spontaneous preterm delivery prior to 32 weeks was 14.1 (95% CI: 9.3-21.4) times higher for women who tested positive for fetal fibronectin compared to those who tested negative. [23] Fetal fibronectin, a protein of the placental membranes, is thought to indicate a disruption to the maternal-fetal interface caused by infection or inflammation when found in cervical secretions between 22 and 34 weeks gestation. [9]

Bacterial vaginosis (BV), a disruption in the vaginal flora, has also been associated with increased risk for preterm spontaneous labor. [24] A multi-center trial of treatment for BV, however, found no effect on reducing rates of preterm delivery suggesting that BV may be a marker of infection of inflammation but not a cause of preterm delivery. [25] Thompson, et al found that inflammatory cells, predominantly neutorphils and macrophages, infiltrated the human myometrium during spontaneous labor at term and likely play a key role in initiating spontaneous preterm labor. [26]

Thus infection and inflammation have been consistently associated with preterm delivery and LBW but the mechanisms have not been clearly identified. This association, especially for very preterm or very low birth weight infants, suggests that perhaps some women with a history of preterm labor develop a susceptibility to dysregulation of inflammation that persists and could be associated with coronary heart disease risk later in life. [27]

1.2.2. Epidemiology of cardiovascular disease in women

Cardiovascular disease is the leading cause of mortality among women in the U.S., causing more deaths than all forms of cancer combined. [13] A total of 456,064 women died from cardiovascular disease in 2002, accounting for 38.3% of all deaths. Women on average experience cardiovascular mortality about ten years later than men, [28] and women's risk for cardiovascular disease increases dramatically after the menopause suggesting that endogenous estrogen may play a protective role in women of reproductive age. It became common clinical practice for postmenopausal women to be prescribed exogenous estrogen during the 1990s due to observational studies that suggested a cardioprotective benefit. However, the landmark Women's Health Initiative trial demonstrated that exogenous hormone replacement therapy in fact increased a woman's risk for cardiovascular mortality [29], indicating there is much yet to learned about women's cardiovascular risks.

There is evidence that cardiovascular risk factors that are elevated in women prior to menopause increase proportionally post menopause. [30] Thus, women who have elevated blood pressure, LDL cholesterol, triglycerides and BMI and low levels of HDL before menopause remain the highest risk after menopause. This evidence suggests that although cardiovascular risk increases dramatically for women after the menopause, high risk women can be identified in the pre- or peri-menopausal years.

Recent work that pooled results from 14 randomized trials demonstrated that 80 to 90% of women and men with CHD have one or more of the conventional risk factors: smoking, diabetes, hyperlipidemia or hypertension. [31] Although the risk factors for cardiovascular disease are the same for women and men, their prevalence and magnitude appear to differ. Isolated systolic hypertension is of particular concern for older women, [32] and diabetes, low HDL cholesterol and obesity are "meshed together in a tight metabolic complex" that appears to

confer a higher CHD risk in women than men. [33] While diabetes increases coronary heart disease risk for women 3 to 7-fold, the magnitude of the risk is decreased to 2 to 3-fold in men. [34] It also appears that while smoking is a risk factor for both men and women, relative risk for stroke in women who smoke is 2.12 while the comparable risk for men who smoke is 1.64. [35]

Women experience a higher fatality rate following a first myocardial infarction. 44% of women will have died within one year post-MI compared to 27% of men. [36] This may be due to increase severity of illness, as women present with disease at an advanced age and with more co-morbidities. Despite an overall decline in the cardiovascular death rate in the U.S. over the past several decades, the rate of decline has been slower for women compared to men, and less for black women compared to white women. In addition, the death rate from cardiovascular disease is 69% higher in black women compared to white women. Two-thirds of sudden deaths due to coronary heart disease occur in women with no previous symptoms, compared to half of sudden deaths in men. [32] These data suggest that primary prevention and early detection of cardiovascular disease in women are needed.

1.2.3. Reproductive history and cardiovascular disease

There are profound changes in a woman's cardiovascular and renal systems to accommodate a normal pregnancy, many of which would be considered signs of cardiovascular dysfunction during any other time. Blood volume increases progressively from 6 to 8 weeks gestation, peaking at an increase of 45 percent by 32 weeks. [37] Cardiac output increases by 30 to 50 percent during pregnancy, with half of this increase occurring very early in pregnancy. In addition, pulse rate increases about 17 percent, and there are striking alterations in renal physiology. Although the insulin response to glucose is augmented in early pregnancy, insulin

resistance emerges during the second half of pregnancy. [38] Serum cholesterol increases are generally greater than 50 percent during pregnancy, accompanied by increases in triglycerides, phospholipids, and lipoproteins. [39] These increases approach the levels found in patients with coronary heart disease. It has also been documented that normal pregnancy is associated with inflammatory changes often as intense as those found in sepsis. [40] Some women may not successfully adapt to these profound changes required to maintain a healthy pregnancy, suggesting that pregnancy provides a 'stress' test of maternal lipid pathways and vascular function. [15] Adverse pregnancy outcomes such as LBW or preterm delivery may in part result from this maladaptation, and could be an indicator of an underlying predisposition for future metabolic or vascular disease.

There is evidence that parity and age at first birth are also associated with cardiovascular risk in women. Ness, et al, examined data from two large cohorts of women and found that high parity (six or more pregnancies) was associated with an increase in risk for cardiovascular disease. [41] It was hypothesized that insulin resistance may play a role in this association, as it is a major risk factor for cardiovascular disease in women.

Several studies have demonstrated that levels of HDL cholesterol are reduced after pregnancy below pre-pregnancy levels, and remain significantly lower in women with multiple pregnancies. [42, 43] It has also been suggested that there may be long term effects of pregnancy on fat distribution and obesity that could affect cardiovascular disease risk, [44-46] and that these associations may differently affect black and white women. [46]

Three studies that examined age at first birth found that women who delivered a first birth before age 20 had an increased risk for coronary heart disease compared to women who were older.[47-49] Although this has been a consistent finding, no biologic mechanisms have

been suggested. It has been hypothesized that young maternal age may be a marker of other sociodemographic risks that are difficult to adequately adjust for, but this has not been investigated. One case control study demonstrated that women who were younger than age 20 at their first birth and had five or more pregnancies had a 2.3-fold higher risk for myocardial infarction compared to women who were older at their first birth and had fewer pregnancies. [49]

The literature on parity and cardiovascular risk suggests that pregnancy has a modest but consistent impact women's long term cardiovascular health. This body of research also indicates that any possible effect must be examined in older women. Research is conflicting when limited to studying cardiovascular disease in younger cohorts of women, perhaps due to the fact that risk for women accelerates after menopause. [50] Our study will examine the possible association of specific reproductive exposures (low birth weight and preterm delivery) and cardiovascular risk in older women. Adjustment will be made for parity and age at first birth along with traditional cardiovascular risk factors.

1.2.3.1. Preeclampsia and maternal cardiovascular risk

There has been extensive investigation of the long term prognosis of women who develop preeclampsia during pregnancy. This work can provide a model for examining how other reproductive exposures, such as low birth weight delivery, may be associated with a woman's long term risk for chronic disease.

Preeclampsia is a pregnancy disorder characterized by increase in blood pressure and proteinuria; eclampsia occurs when seizures are also present. Preeclampsia is a leading cause of maternal mortality in the US, and results from a combination of factors including abnormal implantation and reduced placental perfusion which then ultimately affects maternal organ perfusion.

Roberts and Lain have noted that the maternal risk factors for preeclampsia are similar to those for CVD: diabetes, hypertension, obesity, and insulin resistance. [51] Chesley found that women with eclampsia only in the first pregnancy had no increased risk for chronic hypertension, [52] but women with recurrent preeclampsia had an excess risk for hypertension after 30 years of follow up. He also found that both primiparous as well as multiparous black women with eclampsia had mortality rates 2 to 9 times that of white women, perhaps due to higher underlying rates of hypertension among black women. Sibai found an increased risk for chronic hypertension (14.8%) among women with severe preeclampsia compared to women with normotensive pregnancies (5.6%). [53] The differences were particularly profound for women who developed preeclampsia prior to 30 weeks gestation (OR 2.3) and those who had recurrent preeclamptic pregnancies (OR 7.4). In addition, women who remained normotensive for all pregnancies had the lowest incidence of chronic hyptertension (1.8%).

These studies demonstrate that when pre-eclampsia occurs early in pregnancy or recurs there is an excess risk of future maternal cardiovascular morbidity and mortality. In addition, women with recurrent preeclampsia also have impaired endothelial function [54] and higher diastolic blood pressures, smaller-sized low density lipoproteins, increased apolipoprotein B, and decreased HDL cholesterol compared with their matched controls. [55] Ness, et al, found that women with a family history of cardiovascular disease had an increased risk to develop preeclampsia (OR 1.9) and hypertension during pregnancy. [56] These results suggest that preeclampsia may be at least in part caused by the same factors that contribute to cardiovascular disease later in life.

Ness and Roberts have suggested that preeclampsia may have two distinct origins, each with its own pathologic characteristics and natural history. [57] One results from reduced

placental perfusion, and another from maternal pre-existing but possibly sub-clinical disorders that parallel the risk factors for atherosclerosis and cardiovascular disease. Women with recurring preeclampsia are likely to have underlying risk factors, whereas preeclampsia occurring only in first pregnancies may be more related to reduced placental perfusion. It is possible that a similar heterogenous model may be applied to women who deliver a preterm or low birth weight infant, such that a preexisting disposition for cardiovascular risk converges with other factors to increase the risk for preterm delivery or LBW. Our study will examine this hypothesis in a racially diverse cohort of women, as it is possible that this risk may be different in white and black women.

1.2.3.2. Fetal origins vs. chronic disease model

Due to an ecologic association between high rates of infant mortality and high rates of adult ischemic heart disease death in England and Wales, Barker hypothesized in 1986 that altered growth *in utero*, as reflected in lower birth weight, triggers a biologic adaptation to nutritional deprivation that predisposes an individual to heart disease, obesity and diabetes. [58] Subsequent studies of this fetal origins hypothesis have measured an inverse relationship between infant birth weight and adult risk for chronic disease. This effect has been found consistently for blood pressure, with an estimated 2-4 mm Hg lower systolic blood pressure in adults for every 1 kg increase in their birth weight. [59] Associations between birth weight and adult risk for insulin resistance, type 2 diabetes, [60] and CHD have also been reported. [61]

Alternatively, or additionally, it is possible that familial aggregation of risk for chronic disease, with genetic or environmental components, might explain what has been viewed as the effects of *in utero* undernourishment. [62] This may be particularly true for developed countries where the likelihood of starvation or malnourishment is diminished, and yet rates of LBW,

preterm delivery and cardiovascular disease persist. It is important to understand the mechanisms by which LBW may be associated with long term risk for cardiovascular morbidity and mortality. The fetal origins hypothesis would lead to interventions focused on prenatal and childhood nutrition. In contrast, the chronic disease model would indicate maternal interventions to address risk factors for cardiovascular disease such as hypertension, obesity, insulin resistance and dyslipidemia. The current study is designed to describe the long term prognosis of women who delivered a LBW infant, and builds on relatively recent research that has found an association between delivery of a LBW infant and increased maternal cardiovascular risk.

1.2.3.3. Common risk factors for low birth weight, preterm delivery and cardiovascular disease

The following table summarizes data from multiple studies that identify the risk factors for LBW, IUGR and preterm delivery and categorizes those that are commonly associated with cardiovascular disease. Each of these could be a common pathway by which cardiovascular and pregnancy risks are elevated. Similar to the multifactorial model to explain preeclampsia, a woman's underlying risk for chronic disease could affect some of the pathways leading to LBW and preterm delivery, in particular those that have been associated with both cardiovascular disease and poor pregnancy outcomes.

Table 3: Selected studies of risk factors for low birth weight, preterm delivery and cardiovascular disease in women

Risk factor		Low birth weight	Growth Restriction	Preterm delivery
Associated with cardiovascular disease				
	Black race	2.4 (1.9-2.9) [63] 1.92 (1.64-2.26) a [64] 2.26 (1.39-3.54) b [64]	2.6 (1.82-3.71) [65]	1.79 (1.55-2.08) [66] 2.10 (1.33-3.3) [67] 2.35 (1.72-3.22) c [66]
	Inflammation/Infection			2.9(1.5-5.5) d [23] 3.4 (2.1-5.4) e [23]
	Smoking		1.43 (1.22-1.68) f [68] 2.08 [11] 2.63 (1.77-3.90) g [68] 3.18 (2.06-4.91) [65]	1.24 [11] 1.24 (1.06-1.44) h [66] 2.12 (1.55-2.89) i [66]
	Hypertension	1.99 (1.93-2.06) k [69] 3.58 (3.39-3.79) l [69]	2.07 (1.35-3.18) [65]	
	Non-gestational diabetes			3.84 [11]
	Obesity (BMI >28.8)		1.58 [11]	
	First birth <20			2.91 (1.32-6.45) j [67] 1.29 (1.05-1.59) k [66]
Not typically associated with cardiovascular disease				
	Previous preterm delivery			2.7 (2.1-3.4) [23]
	Incompetent cervix			6.15 (1.79-21.26) [67]
	Drug use			3.9 (1.64-9.26) [67]

Adjusted relative risks or odds ratios (95% CI, when available), [reference]

a Black vs. White, low income

b Black vs. White, moderate income

c Very preterm (24-32 weeks) vs. term

d Fetal fibronectin positive vs. negative, nulliparous women

e Fetal fibronectin positive vs. negative, multiparous women

f Any vs. none for women age 16-17

g Any vs. none for women age 40+

h 1+pack/day vs. none and <37 weeks

i 1+pack/day vs. none and 24-32 weeks

j Maternal age < 20 vs. >=20, Black women

k Maternal age < 20 vs. >= 20, White women

1.2.3.4. LBW and preterm delivery associated with cardiovascular disease risk

There have been five registry-based cohort studies that have detected an association between LBW, preterm delivery and cardiovascular mortality. In 1997 Smith, et al found that parents' overall mortality, as well as cardiovascular mortality, was inversely associated with the birth weights of their offspring. [70] Risk for cardiovascular mortality doubled for mothers (95% CI 1.18 to3.33) for each kilogram decrease in offspring birth weight; relative risk for fathers was 1.52 (95% CI 1.03 to 2.17). The authors concluded that mortality was influenced by factors related to birth weight that were transmissible across generations.

This initial study was replicated in 2000 utilizing a large birth and mortality dataset from England and Wales. Smith, et al [2] found a per kilogram relative risk for cardiovascular mortality strikingly similar to that found in the previous study (RR 2.22, 1.46-3.38). Relative risk for cardiovascular mortality after delivering a LBW infant was 7.05 (2.64-18.77). This study was then replicated in a Finnish cohort that also included data on gestational age. Preterm delivery was associated with a hazard ratio of 2.06 (1.22-3.47) for cardiovascular mortality. [4]
A large cohort study of 676,272 women from Norway designed to determine the long term effects of preeclampsia found similar results. Irgens, et al [3] reported a 2.95-fold increase (95% CI 2.12-4.11) in cardiovascular mortality for women who delivered preterm, but without the additional complication of preeclampsia (median 13 years after delivery).

Smith, et al [1] studied 129,920 deliveries and found independent risks for ischemic heart disease death or hospitalization with preterm delivery (1.8; 95% CI 1.3-2.5) and LBW (4.3; 95% CI 2.9-6.2). Risk for ischemic heart disease death was 11.3 (95% CI 3.5-36.1) for women who delivered a LBW infant compared to a normal weight infant. The authors also found that the

effects were additive, as women who had infants that were both LBW and preterm had a 3.9-fold increase in risk (95% CI 2.2-6.8) of ischemic heart death or hospitalization compared to women with normal weight infants born on time.

Only three studies have related infant birth weight to later occurrence of maternal cardiovascular risk factors, but the results have been consistent. Infant birth weight was inversely related to maternal systolic blood pressure [71, 72] and insulin resistance [71], but there was no association between infant birth weight and later maternal lipid levels. [70, 71]

Most of these studies have utilized large data sets of birth data matched to mortality data, and therefore have had limited ability to adjust for potential confounders such as smoking status and lifetime weight gain. Only a few have involved vascular and metabolic risk factor data, and mean follow up was ten to twenty years. Our study will build on these findings and potentially contribute new information regarding older women with longer follow up, and involve well characterized cardiovascular risk measures and disease status.

1.3. LITERATURE CITED

1. Smith, G., J. Pell, and D. Walsh, *Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births.* Lancet, 2001. **357**(9273): p. 2002-6.
2. Davey Smith, G., S. Harding, and M. Rosato, *Relation between infants' birth weight and mothers' mortality: prospective observational study.* BMJ, 2000. **320**(7238): p. 839-40.
3. Irgens, H., et al., *Long term mortality of mothers and fathers after pre-eclampsia: population based cohort.* BMJ, 2001. **323**(7323): p. 1213-17.
4. Davey Smith, G., et al., *Birth dimensions of offspring, premature birth, and the mortality of mothers.* Lancet, 2000. **356**: p. 2066-67.
5. Institute of Medicine, *Preventing low birth weight*. 1985, Washington, DC: National Academy Press.
6. Klebanoff, M., et al., *Low birth weight across the generations.* JAMA, 1984. **252**(17): p. 2423-7.
7. McCormick, M., *The contribution of low birth weight to infant mortality and childhood morbidity.* NEJM, 1985. **312**: p. 82-90.
8. Iams, J. and R. Creasy, *Preterm labor and delivery*, in *Maternal and Fetal Medicine: Principles and Practice*, R. Creasy and R. Resnic, Editors. 2004, Saunders: Philadelphia. p. 623-61.
9. Iams, J., R. Goldenberg, and B. Mercer, *The preterm prediction study: recurrent risk of spontaneous preterm birth.* Am J Obstet Gynecol, 1998. **178**: p. 1035-40.
10. Mattison, D., et al., *Preterm delivery: a public health perspective.* Paediatric Perinatal Epidemiology, 2001. **15**(supplement): p. 7-16.
11. Zeitlin, J., et al., *Are risk factors the same for small for gestational age versus other preterm births.* Am J Obstet Gynecol, 2001. **185**(1): p. 208-15.
12. Resnik, R. and R. Creasy, *Intrauterine Growth Restriction*, in *Maternal and Fetal Medicine: Principles and Practices*, R. Creasy and R. Resnik, Editors. 2004, Saunders: Philadelphia. p. 495-512.
13. National Center for Health Statistics, *Health, United States*. 2004.
14. National Center for Health Statistics, *Births: Final data for 2002*. 2002. p. 114.
15. Sattar, I. and I. Greer, *Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening?* BMJ, 2002. **325**: p. 157-160.
16. Wang, X., et al., *Familial aggregation of low birth weight among whites and blacks in the United States.* NEJM, 1995. **333**: p. 1744-1749.
17. Sheppard, B. and J. Bonnar, *The ultrastructure of the arterial supply of the human placenta in pregnancy complicated by fetal growth restriction.* Br J Obstet Gynaecol, 1976. **83**: p. 948-59.
18. Germain, A., et al., *Preterm labor: placental pathology and clinical correlation.* Obstetrics and Gynecology, 1999. **94**(284-289).
19. Roberts, J. and D. Cooper, *Pathogenesis and genetics of pre-eclampsia.* Lancet, 2001. **357**: p. 53-56.
20. Benowitz, N., *Nicotine replacement therapy during pregnancy.* JAMA, 1991. **266**: p. 3174-3177.
21. Goldenberg, R., J. Hauth, and W. Andrews, *Mechanisms of disease: intrauterine infection and preterm delivery.* NEJM, 2000. **342**(20): p. 1500-7.

22. Korn, A., et al., *Plasma cell endometritis in women with symptomatic bacterail vaginosis.* Obstetrics and Gynecology, 1995. **85**(387-90).
23. Goldenberg, R., J. Iams, and B. Mercer, *The preterm prediction study: the value of new vs. standard risk factors.* American Journal of Public Health, 1998. **88**(2): p. 233-8.
24. Hillier, L., et al., *Association between bacterial vaginosis and preterm delivery of a low-birth-weight infant.* NEJM, 1995. **333**: p. 1737-1742.
25. Carey, J., et al., *Metronidazole to prevent preterm delivery in pregnant women with asymptomatic bacterial vaginosis.* NEJM, 2000. **342**(8): p. 534-40.
26. Thomson, A., et al., *Leukocytes infiltrate the myometrium during human parturition: further evidence that labour is an inflammatory process.* Human Reproduction, 1999. **14**(1): p. 229-36.
27. Ridker, P., et al., *C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women.* NEJM, 2000. **342**(12): p. 836-43.
28. Labarthe, D., *Epidemiology and Prevention of Cardiovascular Disease: A Global Challenge*. 1998: Aspen Publications.
29. Writing group for the Women's Health Initiative Investigators, *Risks and benefits of estrogen plus progestin in healthy postmenopausal women.* JAMA, 2002. **288**(3): p. 321-33.
30. Matthews, K., et al., *Changes in cardiovascular risk factors during the perimenopause and postmenopause and carotid artery atherosclerosis in healthy women.* Stroke, 2001. **32**(5): p. 1104-11.
31. Khot, U., et al., *Prevalence of conventional risk factors in patients with coronary heart disease.* JAMA, 2003. **290**(7): p. 898-904.
32. Mosca, L., et al., *Cardiovascular disease in women: a statement for healthcare professionals from the American Heart Association.* Circulation, 1997. **96**(7): p. 2468-82.
33. Gordon, T., et al., *Diabetes, blood lipids, and the role of obestiy in coronary heart diease risk for women. The Framingham Study.* Annals of Internal Medicine, 1977. **87**(4): p. 393-7.
34. Manson, J. and A. Spelsberg, *Risk modification in the diabetic patient*, in *Prevention of Mycardial Infarction*, J. Manson, et al., Editors. 1996, Oxford University Press: New York, NY. p. 249-250.
35. Njolstad, I., E. Arnesen, and P. Lund larsen, *Body height, cardiovascular risk factors, and risk of stroke in middle-aged men and women: a 14-year follow up study of the Finnmark Study.* Circulation, 1996. **94**: p. 2877-2882.
36. Kannel, W. and P. Wilson, *Risk factors that attenuate the female cornary disease advantage.* Archives of Internal Medicine, 1995. **155**: p. 57-61.
37. Monga, M., *Maternal cardiovascular and renal adaptation to pregnancy*, in *Maternal and Fetal Medicine: Principles and Practice*, R. Creasy and R. Resnik, Editors. 2004, Saunders: Philadelphia. p. 111-20.
38. Nuwayhid, B., T. Nguyen, and A. Khraibi, *Maternal physiology*, in *Essentials of Obstetrics and Gynecology*, N. Hacker and J. Moore, Editors. 1998, Saunders Company: Philadelphia. p. 85-99.
39. Schwertner, H., et al., *Cortisol and the hypercholesterolemia of pregnancy and labor.* Atherosclerosis, 1987. **67**: p. 237-244.

40. Sacks, G., et al., *Normal pregnancy and preeclampsia both produce inflammatory changes in peripheral blood leukocytes akin to those of sepsis.* JAMA, 1998. **179**(1): p. 80-6.
41. Ness, R., et al., *Number of pregnancies and the subsequent risk of cardiovascular disease.* NEJM, 1993. **328**(21): p. 1528-1533.
42. Flegal, K., R. Ness, and R. Dramer, *Parity and high density lipoprotein (HDL) cholesterol levels in white women from the Second National Health and Nutrition Examination Survey (NHANES II). (Abstract).* American Journal of Epidemiology, 1990. **132**: p. 766.
43. Kritz-Silverstein, D., E. Barrett-Connor, and D. Wingard, *The relationship between multiparity and lipoprotein levels in older women.* J Clin Epidemiology, 1992. **45**(7): p. 761-67.
44. denTonkelaar, I., et al., *Fat distribution in relation to age, degree of obesity, smoking habits, parity, and estrogen use: a cross-sectional study in 11,825 Dutch women participating in the DOM-project.* Int J Obesity, 1990. **14**(9): p. 753-61.
45. Kaye, S., et al., *The association of body fat distribution with lifestyle and reproductive factors in a population study of postmenopausal women.* Int J Obesity, 1990. **14**(7): p. 583-91.
46. Forster, J., et al., *Reproductive history and body mass index in black and white women.* Prev Med, 1986. **15**(6): p. 685-91.
47. Beard, C., V. Fuster, and J. Anneggers, *Reproductive history in women with coronary heart disease: a case-control study.* Am J Epidemiol, 1984. **120**(1): p. 108-114.
48. LaVecchia, C., et al., *Menstrual and reproductive factors and the risk of myocardioal infarction in women under fifty-five years of age.* Am J Obstet Gynecol, 1987. **157**(15): p. 1108-12.
49. Palmer, J., L. Rosenberg, and S. Shapiro, *Reproductive factors and risk of myocardial infarction.* Am J Epidemiol, 1992. **136**(4): p. 408-416.
50. Ness, R., et al., *Reproductive history and coronary heart disease risk in women.* Epidemiology Reviews, 1994. **16**(2): p. 298-314.
51. Roberts, J. and K. Lain, *Recent insights into the pathogenesis of pre-eclampsia.* Placenta, 2002. **23**: p. 359-372.
52. Chesley, L., J. Annitto, and R. Cosgrove, *The remote prognosis of eclamptic women: sixth periodic report.* Am J Obstet Gynecol, 1976. **124**: p. 446-59.
53. Sibai, B., A. El-Nazer, and A. Gonzalez-Ruiz, *Severe preeclampsia in young primigravid women: subsequent pregnancy outcome and remote prognosis.* Am J Obstet Gynecol, 1986. **155**: p. 1011-6.
54. Chambers, J., et al., *Association of maternal endothelial dysfunction with preeclampsia.* JAMA, 2001. **285**(12): p. 1607-12.
55. Hubel, C., et al., *Dyslipoproteinaemia in postmenopausal women with a history of preeclampsia.* Fr J Obstet Gynaecol, 2000. **107**(776-84).
56. Ness, R., et al., *Family history of hypertension, heart disease, and stroke among women awho develop hypertension in pregnancy.* Obstetrics and Gynecology, 2003. **102**(6): p. 1366-71.
57. Ness, R. and J. Roberts, *Heterogeneous causes constituting the single syndrome of preeclampsia: a hypothesis and its implications.* Am J Obstet Gynecol, 1996. **105**: p. 1365-70.

58. Barker, D. and C. Osmond, *Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales.* Lancet, 1986. **8489**(1): p. 1077-81.
59. Law, C. and A. Shiell, *Is blood pressure inversely related to birth weight? The strength of the evidence from a systematic review of the literature.* Journal of Hypertension, 1996. **14**(935-41).
60. Eriksson, J., et al., *Effects of size at birth and childhood growth on insulin resistance syndrome in elderly individuals.* Diabetologia, 2002. **45**(3): p. 342-8.
61. Forsen, T., et al., *Growth in utero and during childhood among women who develop coronary heart disease: longitudinal study.* BMJ, 1999. **319**: p. 1403-7.
62. Henriksen, R. and T. Clausen, *The fetal origins hypothesis: placential insufficiency and inheritancce versus maternal malnutrition in well-nourished populations.* Acta Obstet Gynecol Scand, 2002. **81**: p. 112-14.
63. David, R. and J. Collins, *Differing birth weight among infants of U.S.-born Blacks, African-born Blacks and U.S.-born Whites.* NEJM, 1997. **337**(17): p. 1209-1214.
64. Collins, J. and R. David, *The differential effect of traditional risk factors on infant birthweight among Blacks and Whites in Chicago.* Am J Public Health, 1990. **80**: p. 679-81.
65. Abrams, B. and V. Newman, *Small-for-gestational age birth: maternal predictors and comparison with risk factors of spontaneous delivery in the same cohort.* Am J Obstet Gynecol, 1991. **164**: p. 785-90.
66. Shiono, P. and M. Klebanoff, *Ethnic differences in preterm and very preterm delivery.* Am J Public Health, 1986. **76**(11): p. 1317-21.
67. Abrams, B., et al., *Maternal weight gain and preterm delivery.* Obstetrics and Gynecology, 1989. **74**: p. 577-83.
68. Fox, S., T. Koepsell, and J. Daling, *Birth weight and smoking during pregnancy-effect modification by maternal age.* Am J Epidemiol, 1994. **139**: p. 1008-15.
69. Fang, J., S. Madhavan, and M. Alderman, *The influence of maternal hypertension on low birth weight: differences among ethnic populations.* Ethnicity and Disease, 1999. **9**(369-76).
70. Davey Smith, G., et al., *Birth weight of offspring and mortality in the Renfrew and Paisley study: prospective observational study.* BMJ, 1997. **315**(717): p. 1189-1193.
71. Lawlor, D., G. Davey Smith, and S. Ebrahim, *Birth weight of offspring and insulin resistance in late adulthood: cross sectional survey.* BMJ, 2002. **325**: p. 359-62.
72. Walker, B., et al., *Contribution of parental blood pressures to association between low birth weight and adult high blood pressure: cross sectional study.* BMJ, 1998. **316**: p. 834-7.

2. ARTICLE ONE: ACCURACY AND RELIABILITY OF MATERNAL RECALL OF INFANT BIRTH WEIGHT AMONG OLDER WOMEN

2.1. ABSTRACT

Maternal recall of infant birth weight provides a cost-effective and efficient way to obtain pregnancy-related data, and it is often the only source available among older women. We assessed the accuracy and reliability of maternal recall of infant birth weight 35 to 70 years after delivery. Participants were 119 well functioning women (mean age 80 years; 47.5% black) randomly selected from participants at the Pittsburgh, Pennsylvania field center of the Study of Health, Aging and Body Composition (Health ABC), a prospective study of body composition changes and morbidity. Women were asked via phone to report the birth weight for each pregnancy lasting more than six months. Women who then provided documentation of birth weights comprised the validity sample (n=22). Women who reported birth weights a second time in person comprised the reliability sample (n=98). Women in the validity and reliability samples were not different in terms of race, education, income or age at first birth from the remaining women in the cohort (n=349) who reported at least one birth. In the validity sample, agreement between recalled and documented birth weights was high for first births (ICC=0.96), but lower for higher order births (ICC=0.59). Recalled birth weights for first births were underestimated by 44 g (SD 136 g); higher order births were underestimated by 86g (SD 345 g). In the reliability sample, maternal recall was highly reliable for first births (r=0.95) and higher order births (r=0.87). Reliability of recall for first births remained high when considered separately by race, education, income and age. Women report accurate and reliable infant birth weight data an average of 57 years after delivery, and recall is particularly precise for first births.

2.2. INTRODUCTION

The reproductive history of older women can provide important information to investigate relationships between pregnancy exposures and maternal health outcomes. Several studies have linked delivery of a low birth weight infant with increased maternal risk for cardiovascular death, [1-4] and inter-generational studies have demonstrated that low birth weight, like cardiovascular disease, aggregates in families. [5, 6]

Hospital or state delivery records with documented infant birth weight are often not available for deliveries occurring prior to 1950, making retrospective studies involving certain reproductive exposures of older women challenging. Maternal recall of infant birth weight provides a cost-effective and efficient way to obtain these data, and it is often the only source available. Previous studies of maternal recall of infant birth weight have focused predominantly on the accuracy of short-term recall [7-13], and one study investigated the accuracy and reliability of maternal recall of births that occurred, on average, 32 years in the past.[14] The purpose of this study is to assess the accuracy and reliability of maternal recall of infant birth weight 35 to 70 years after delivery.

2.3. METHODS

2.3.1. Participants

The Health, Aging and Body Composition (Health ABC) Study is a large on-going epidemiologic study of how changes in body composition affect morbidity, disability, and mortality. A total of 3,075 community dwelling participants (50% female) were enrolled in Pittsburgh, Pennsylvania and Memphis, Tennessee in 1997-1998. Recruitment procedures have been described elsewhere in detail.[15] Eligibility criteria included: age 70 to 79; self-report of no difficulty walking one quarter mile or climbing 10 steps without resting; no difficulty performing basic activities of daily living; no use of assistive devices to ambulate; no history of active treatment for cancer in the prior three years; and no plans to move out of the area in the next three years. Based on these criteria participants are considered well functioning.[16] All participants signed an informed consent approved by the institutional review board at the University of Pittsburgh.

2.3.2. Accuracy and reliability samples

Among 608 women in the Pittsburgh cohort who were interviewed in 2003 and 2004 as part of on-going follow-up, we included questions about pregnancy history. Of the 597 women (98%) who provided pregnancy history details, 507 (85%) had at least one live birth.

A total of 142 women were randomly selected for clinic visits in addition to phone interviews, and these women were first contacted via phone to complete pregnancy history questions. They were then scheduled for a clinic visit and asked to bring documentation of infant birth weight in the form of hospital records, birth certificates or other commonly maintained family documentation. Among 119 women (84%) who attended the clinic and provided pregnancy data both via phone and in person, 22 (18.5%) provided documentation of at least one birth weight. Evidence provided was reviewed by study personnel and deemed to be created at or near the time of delivery. These 22 women comprised the accuracy sample.

Birth weights were gathered a second time via recall during the clinic visit from the remaining 98 women unable to provide birth weight documentation; an average of two weeks elapsed between phone recall and in person recall. These 98 women comprised the reliability sample.

2.3.3. Statistical analysis

Women comprising the accuracy and reliability samples were compared to the remaining cohort of women with at least one reported birth weight to ensure that they were representative. Characteristics compared were age, race, education, income, smoking status, age at first birth, number of live births, and mean infant weight of the first birth. The chi square test of independence and the student t test for independent samples were used to detect differences in proportions and means between the groups.

For the accuracy study, we calculated an intraclass correlation coefficient (ICC) between the recalled and documented birth weight data. An ICC greater than 0.8 was considered a strong correlation. [17, 18] An ICC was calculated separately for first births and for higher order births.

We also investigated the correspondence between categories of birth weight when recalled and documented, as we suspected that women may be able to recall infant birth weight more accurately as a categorical vs. continuous variable. Birth weights were characterized into low (<2500 g), normal (2500-3500) and high (>3500 g). Agreement between classification via recall and classification via documentation was evaluated utilizing the kappa statistic. A kappa greater than 0.8 was considered excellent agreement, between 0.61 and 0.8 was considered substantial agreement, and between 0.41 and 0.6 was considered moderate agreement.[19] Since a low kappa value may reflect a low prevalence of a trait in the population rather than lack of agreement [20], the proportion of positive agreement was also calculated.

For the recall study, the two reports of maternal recall were compared using Pearson correlation coefficients, calculated separately for first versus higher order births. Correlation coefficients were also stratified by race, education, and income.

2.4. RESULTS

A total of 469 women interviewed provided at least one child's birth weight, collected in pounds and ounces and transformed into grams for purposes of analysis. Mean age at this interview was 80, and 47% of women were black. On average, 56.6 years (SD 5 years) had elapsed between delivery of the first birth and age at the time of the interview.

There were no significant differences between women in the accuracy and reliability samples in terms of education, income or age at first birth when they were compared to the remaining women interviewed (Table 4). There were slightly more black women in the accuracy sample and the women in the accuracy and reliability samples were somewhat less likely to have ever smoked. The women in the accuracy and reliability samples were marginally younger than the remaining women interviewed (p-value=0.069) and they had more live births (p-value=0.001).

2.4.1. Accuracy

There were 22 women who provided birth weight documentation for 40 live births; 14 were for first births. Documentation sources included hospital records (50%), baby books with dated birth weights (33%), birth certificates (10%) and other sources (7%). Agreement between recalled and documented birth weights was very high for first births (ICC=0.96), but lower for higher order births (ICC=0.59) (Figure 1). Agreement between recalled and documented birth weights for all births combined was moderate (ICC=0.77). Recalled weight for first births was underestimated on average by 44 g (SD 136 g). Higher order births were underestimated by 86 g. (SD 345 g).

Mothers successfully classified first births into low (<2500 g), normal (2500-3500 g) and high (>3500 g) birth weight categories (Kappa=0.83; 95% CI: 0.51-1.00). Proportion of positive agreement was 0.93 for first births. There was moderate agreement between classification of higher order births based on recalled and documented weights (r=0.58, 95% CI: 0.28-0.88). The proportion of positive agreement was 0.81 for higher order births.

2.4.2. Reliability

Among the 98 women who reported birth weights twice via recall, maternal recall of infant weight for first births (n=95) was highly reliable (r=0.95). Correlation between the two instances of recall for higher order births (n=227) was 0.87, and overall reliability for all births combined was high (r=0.90). Reliability of recall for first births remained high when considered separately by race, education, income and age (Table 5). Reliability dropped for higher order births across all groups, except for the lowest income group. The correlation coefficient dropped to 0.67 for higher order birth weights recalled among women with less than a high school education, but remained high (r=0.94) for first births recalled by this group of women.

2.5. DISCUSSION

Our results confirm that women report accurate and reliable infant birth weight data an average of 57 years after delivery. To our knowledge, accuracy and reliability of maternal recall of infant birth weight this long after the delivery has not previously been reported. Our results, however, are consistent with those of Tomeo, et al [14] who found that maternal recall of infant birth weight an average of 32 years after delivery was valid and reliable.

Our finding that first births were recalled more accurately than higher order births is also consistent with the one other study that examined this aspect of maternal recall.[10] Previous studies reported that women underestimate birth weight on average 25 to 95 g. [8, 10, 14] Our results were remarkably similar to these.

We also confirmed that older women report infant birth weight reliably across race, age and socioeconomic strata. Although women with less than a high school education had less consistent recall of higher order births, they were still highly reliable sources of information on infant weight for first births.

Our data confirm the appropriateness of relying on maternal recall of infant birth weight in epidemiologic studies, particularly when maternal recall may be the only available source of these data. In a similar study of maternal recall 18 years after delivery, Lumey [11] indicated that use of maternal recall data would attenuate the true association between birth weight and other outcomes of interest. His analysis indicated that a 30% increase in sample size would compensate for the loss of precision resulting from maternal recall of information about infant weights.[11]

There are limitations to our study. Our sample of validated birth weights was small. Hospital and state records with infant birth weights prior to 1950 are not commonly available in Pennsylvania, and this forced us to rely on birth weight records maintained in the home. We found that many women interviewed had given these records to their children or no longer maintained them. Although small, our sample of women with documented infant birth weights was representative of our racially diverse cohort according to education, income and age at first birth. Our results, therefore, are generalizable to well functioning community dwelling older women.

Our reliability analysis only tested the consistency of maternal recall of birth weights collected two weeks apart, the first report collected by phone and the second report collected in person. Our results, however, were remarkably consistent with another study that reported a

high correlation (r=0.94) between maternal recall of infant birth weight collected two years apart among women at a mean age of 78. [14]

Our results confirm the accuracy and reliability of maternal recall of infant birth weight collected on average 57 years after delivery. Birth weight was recalled with particular precision for first births. Maternal recall is a reliable source of information about infant birth weight for first births long after pregnancy, and these data can be valuable for epidemiologic studies linking pregnancy history to chronic disease risk among older women, as well as for inter-generational studies of low birth weight.

Table 4: Comparison of maternal characteristics (% or mean and SD) for accuracy group, reliability group and remaining cohort

		Accuracy (n=22)	Reliability (n=98)	Remaining Cohort (n=349)	p-Value
Age		79.4 (2.4)	79.5 (2.5)	80.2 (2.9)	0.069
Black		54.6%	45.9%	43.6%	0.576
Education					
	Less than high school	18.2%	12.2%	14.9%	0.356
	High school graduate	36.4%	41.8%	49.3%	
	Postsecondary	45.5%	45.9%	35.8%	
Family income					
	Less than $10,000	5.0%	8.4%	14.7%	0.188
	$10,000 to $25,000	40.0%	43.4%	44.7%	
	$25,000 to $50,000	45.0%	30.1%	31.3%	
	$50,000+	10.0%	18.1%	9.3%	
Ever smoked		31.8%	36.7%	46.4%	0.120
Age at first birth		22.7 (3.6) (range: 16-30)	23.6 (4.1) (range: 16-36)	23.5 (4.5) (range: 14-41)	0.689
Number of live births		3.4 (.85) (range: 1-5)	3.5 (1.8) (range: 1-10)	2.9 (1.5) (range: 1-9)	0.001
First birth (weight in g)		3210 (489)	3211 (543)	3082 (596)	0.111

Table 5: Correlation between recalled infant birth weights stratified by race, education, income and age

Characteristic		First births (n=95)	Higher order births (n=227)
Race			
	White	0.953	0.850
	Black	0.957	0.894
Education			
	Less than high school	0.937	0.666
	High school graduate	0.957	0.894
	Postsecondary	0.953	0.916
Family income			
	Less than $10,000	0.918	0.982
	$10,000 to $25,000	0.962	0.848
	$25,000 to $50,000	0.957	0.964
	$50,000+	0.994	0.956
Age			
	Less than 80	0.969	0.845
	80 and older	0.936	0.896

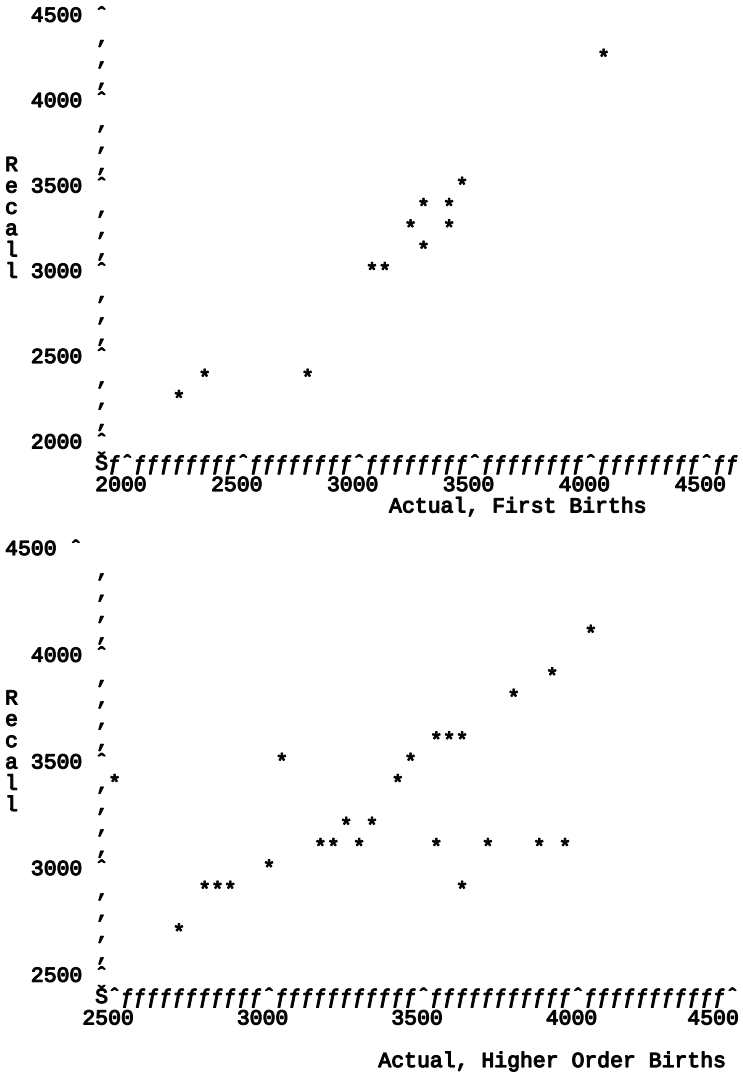

Figure 1: Recalled vs. actual infant birth weight, first births vs. higher order births

2.6. LITERATURE CITED

1. Davey Smith, G., S. Harding, and M. Rosato, *Relation between infants' birth weight and mothers' mortality: prospective observational study.* BMJ, 2000. **320**(7238): p. 839-40.
2. Davey Smith, G., et al., *Birth dimensions of offspring, premature birth, and the mortality of mothers.* Lancet, 2000. **356**: p. 2066-67.
3. Smith, G., J. Pell, and D. Walsh, *Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births.* Lancet, 2001. **357**(9273): p. 2002-6.
4. Irgens, H., et al., *Long term mortality of mothers and fathers after pre-eclampsia: population based cohort.* BMJ, 2001. **323**(7323): p. 1213-17.
5. Klebanoff, M., et al., *Low birth weight across the generations.* JAMA, 1984. **252**(17): p. 2423-7.
6. Wang, X., et al., *Familial aggregation of low birth weight among whites and blacks in the United States.* NEJM, 1995. **333**: p. 1744-1749.
7. Yawn, B., V. Suman, and S. Jacobsen, *Maternal recall of distant pregnancy events.* Journal of Clinical Epidemiology, 1998. **51**(5): p. 399-405.
8. Olson, J., et al., *Medical record validation of maternally reported birth characteristics and pregnancy-related events: a report from the Children's Cancer Group.* Am J Epidemiol, 1997. **145**(1): p. 58-67.
9. Tilley, B., et al., *A comparison of pregnancy history recall and medical records.* Am J Epidemiol, 1985. **121**(2): p. 269-281.
10. Seidman, D., et al., *Accuracy of mothers' recall of birthweight and gestational age.* British Journal of Obstetrics and Gynaecology, 1987. **94**(8): p. 731-5.
11. Lumey, L., A. Stein, and A. Ravelli, *Maternal recall of birthweights of adult children: validation by hospital and well baby clinic records.* Int J Epidemiology, 1994. **23**(5): p. 1006-1011.
13. Lederman, S. and A. Paxton, *Maternal reporting of prepregnancy weight and birth outcome: consistency and completeness compared with the clinical record.* Maternal and Child Health Journal, 1998. **2**(2): p. 123-126.
14. Tomeo, C., et al., *Reproducibility and validity of maternal recall of pregnancy-related events.* Epidemiology, 1999. **10**(6): p. 774-7.
15. Visser, M., et al., *Leg muscle mass and composition in relation to lower extremity performance in men and women aged 70 to 79: the Health, Aging and Body Composition Study.* JAGS, 2002. **50**(5): p. 897-904.
16. Rooks, R., et al., *The association of race and socioeconomic status with cardiovascular disease indicators among older adults in the Health, Aging, and Body Composition Study.* Journal of Gerontology: Social Sciences, 2002. **57B**(4): p. S247-S256.
17. Shrout, P. and J. Fleiss, *Intraclass correlations: uses in assessing rater reliability.* Psychological Bulletin, 1979. **86**(2): p. 420-8.
18. Muller, R. and P. Buttner, *A critical discussion of intraclass correlation coefficients.* Statistics in Medicine, 1994. **13**: p. 2465-76.

19. Landis, J. and G. Koch, *The measurement of observer agreement for categorical data.* Biometrics, 1977. **33**: p. 159-74.
20. Feinstein, A. and D. Cichetti, *High agreement but low kappa: the problem of two paradoxes.* Journal of Clinical Epidemiology, 1990. **1990**(43): p. 6.

3. ARTICLE TWO: ASSOCIATION BETWEEN INFANT BIRTH WEIGHT AND MATERNAL CARDIOVASCULAR RISK FACTORS IN THE HEALTH, AGING AND BODY COMPOSITION STUDY

3.1. ABSTRACT

Mothers who deliver a low birth weight infant may themselves be at excess risk for cardiovascular disease. We investigated whether older women who bore low birth weight (LBW) infants had higher blood pressure, lipids, glucose, insulin, interleukin-6, C-reactive protein concentrations, and higher pulse wave velocity compared to women with normal weight births. Participants were 446 women (mean age 80 years; 47% black) enrolled in the Pittsburgh, PA field center of The Health, Aging and Body Composition Study. Women reported birth weight, smoking status, prematurity, and selected complications for each pregnancy. Analysis was limited to first births not complicated by hypertension or preeclampsia. Women who had delivered a LBW first birth (<2500 g) had a lower current BMI (adjusted for race and age) compared to women with normal weight (2500-3500 g) infants (26.6 vs. 28.0 kg/m^2; p=0.057), but they had a higher abdominal circumference (98.1 vs. 95.0 cm; p=0.007). They were also more likely to be on anti-hypertensive medication (p=0.061). After adjustment for BMI, race and age, women with a history of a LBW infant had higher levels of IL-6 (p=0.021), fasting insulin (p=0.064), and triglycerides (p=0.071), and they were more insulin resistant (p=0.045) compared to women with a normal weight infant. Women who delivered small infants also had elevations in systolic blood pressure (p=0.048), and pulse pressures were marginally elevated compared to women with a normal weight first birth. Women who had delivered infants both LBW and preterm (<37 weeks) had the smallest babies, had higher current waist circumferences

and systolic blood pressures, and had levels of IL-6, CRP, and insulin resistance that were markedly elevated when compared to women with normal weight births. These findings raise the possibility that a history of LBW delivery may identify women who would benefit from screening and intervention around risk factors for cardiovascular disease.

3.2. INTRODUCTION

Mothers who deliver a low birth weight infant may themselves be at excess risk for cardiovascular disease. Large registry-based observational studies found that a low birth weight delivery increased maternal risk for cardiovascular death 7 to 11-fold [1, 2] and that risk for cardiovascular death was 2 to 3 times higher for women who delivered a preterm infant compared to those who had delivered an infant at term.[3, 4] In two studies that related reproductive history to later occurrence of cardiovascular risk factors, bearing a low birth weight infant was inversely related to systolic blood pressure [5, 6] and maternal insulin resistance.[6]

Low birth weight (LBW) and its components, idiopathic preterm delivery and intrauterine growth restriction (IUGR), share many risk factors with cardiovascular disease (CVD). These include black race [7-10], young maternal age [10, 11], inflammation and infection [12], cigarette smoking [10, 11, 13, 14], hypertension [9, 15], and non-gestational diabetes. [13] It has been proposed that unsuccessful adaptation to the profound biologic demands of pregnancy may result in growth restriction and perhaps other causes of LBW, and that the reasons for maladaptation to pregnancy could involve metabolic and vascular disease pathways.[16]

Most studies of LBW and CVD to date have utilized large registries of delivery data matched to mortality data. As such, they have had limited ability to adjust for potential

confounders such as life time smoking exposure and weight gain. Furthermore, they have not characterized outcomes beyond ten to twenty years post partum. We sought to assess the association between delivery of a low birth weight infant and increased cardiovascular morbidity among older women many. Specifically, we investigated whether women who bore low birth weight infants had later elevations in blood pressure, pulse pressure, lipid profiles, glucose, insulin, interleukin-6 (IL-6), C-reactive protein (CRP), and pulse wave velocity.

3.3. METHODS

3.3.1. Participants

The Health, Aging and Body Composition (Health ABC) Study is a large on-going epidemiologic study of how changes in body composition affect morbidity, disability, and mortality. A total of 3,075 community dwelling participants (50% female) were enrolled in Pittsburgh, Pennsylvania and Memphis, Tennessee in 1997-1998. Recruitment procedures have been described elsewhere in detail.[17] All participants signed an informed consent approved by the institutional review board at the University of Pittsburgh. Eligibility criteria included: age 70 to 79; self-report of no difficulty walking one quarter mile or climbing 10 steps without resting; no difficulty performing basic activities of daily living; no use of assistive devices to ambulate; no history of active treatment for cancer in the prior three years; and no plans to move out of the area in the next three years. Based on these criteria participants were considered well functioning.[18]

Among 608 women in the Pittsburgh cohort who were interviewed in 2003 and 2004 as part of the year 7 follow-up visit, we included questions about pregnancy history. 597 women (98%) provided pregnancy history details. Of the 507 (85%) women who had at least one live birth, 466 (92%) provided their first born's birth weight. Mean age at this interview was 80, and 47% of women were black. We excluded women who reported hypertension during pregnancy (n=11) or preeclampsia (n=11) to describe maternal prognosis after delivery of a LBW infant beyond the well known increase in CVD risk for women with these pregnancy complications. [19-24] Results are presented for 446 women.

3.3.2. Recalled birth characteristics

Women were asked to report the birth weight for each pregnancy lasting more than six months. Smoking status, prematurity (early vs. on time and in weeks) as well as selected complications (hypertension during pregnancy and preeclampsia) were also assessed for each pregnancy. Analysis was limited to first births, as birth weight and gestational age are recalled more accurately for first births compared to subsequent births.[25]

Infant birth weight was converted to grams for the purposes of the analysis, and was evaluated as a continuous variable, a dichotomous low birth weight variable (<2500 g vs. >=2500 g), and a categorical variable [low (<2500 g), moderate (2500 to 3500 g), and high (>3500 g)]. LBW was also stratified by preterm delivery (< 37 weeks gestation). This stratification allowed us to identify a subset of deliveries that were small and preterm.

3.3.3. Cardiovascular endpoints

The primary endpoints were cardiovascular risk factors assessed at baseline (1997 to 1998). Blood pressures were measured according to standard protocol [26] and pulse pressures were calculated (systolic blood pressure minus diastolic blood pressure). Total cholesterol, HDL, triglyercerides, and glucose were assayed from fasting serum with colorimetric technique on a Johnson & Johnson Vitros 950 analyzer (New Brunswick, NJ). Serum insulin (non-diabetics only) was determined using a radioimmunoassay kit (Pharmacia, Uppsala, Sweden). Insulin resistance was estimated with the homeostatis model assessment (HOMA), the product of fasting glucose and insulin concentrations in mmol/l divided by 22.5.[27] LDL was estimated with the Friedwald equation, and for hemoglobin A1c ion-exchange high performance liquid chromatography (Biorad Variant analyzer) was used. Measures of the inflammatory markers IL-6, TNF-α, and CRP were obtained from frozen stored serum collected by venipuncture after an overnight fast. Cytokines were measured in duplicate by an enzyme-linked immunosorbent essay kit from R&D Systems (Minneapolis, MN). Serum levels of CRP were also measured in duplicate by enzyme-linked immunosorbent essay based on purified protein and polyclonal anti-CRP antibodies. Blind duplicate analyses showed an average interassay coefficient of variation of 10.3% (IL-6), 8.0% (CRP), and 15.8% (TNF- α).

Aortic pulse wave velocity (aPWV) was assessed as an indicator of aortic stiffness and was measured from simultaneous Doppler flow signals obtained from the right carotid and right femoral arteries by use of nondirectional transcutaneous Doppler flow probes. At least 10 beats were averaged for each simultaneous recording site, and three separate runs were recorded for

each participant. Timing between the onset of flow at the carotid and femoral sites was divided by the associated distance to produce flow velocity.

3.3.4. Statistical analysis

Students t-test or chi-square tests were used to detect differences in means or proportions between women who delivered low birth weight vs. normal weight infants. Characteristics compared included sociodemographic status (race, education, and income), pregnancy history (smoking status during pregnancy, age at first birth), smoking history [characterized as never, former or current and measured in pack years (the average packs of cigarettes smoked daily multiplied by years smoking)], presence of diabetes (physician diagnosed and confirmed with medication), and current use of statins or anti-hypertensives.

Pearson correlation coefficients were calculated to compare the relationship between the birth weight of the first born and continuous endpoints. Inflammatory markers, triglycerides, glucose, insulin, hemoglobin A1c, and aPWV were log-transformed for the purposes of analysis as they were not normally distributed, but results are presented as actual values. Analysis of covariance (ANCOVA) was used to detect differences in the means of body composition variables across three birth weight categories (low, moderate and high), adjusted for race and age. These included BMI (kg/m^2) at study baseline and at ages 25 and 50 (weight reported via recall and height measured at study baseline and adjusted for shrinking [28]); abdominal circumference; and visceral fat (estimated with CT scans between fourth and fifth lumbar vertebrae). ANCOVA was also used to detect differences in means (adjusted for BMI, race, and age) for each cardiovascular risk factor dichotomized into LBW and normal birth weight groups

as there were no significant differences in these factors for women who delivered infants > 3500 g. In secondary analysis current smokers were removed. Moreover, women were stratified by race to determine whether the results differed significantly for black and white women. Deliveries were also stratified into LBW and preterm versus LBW and not preterm. All tests were two-sided and differences with a p-value <0.05 were considered significant; differences <0.1 were considered marginally significant.

3.4. RESULTS

Among the 446 women who recalled the birth weight of their first born (resulting from pregnancies not complicated by hypertension or preeclampsia), mean birth weight was 3117 g (SD 582), and 56 (12.6%) women recalled having a baby of birth weight less than 2500 g. Thirty first births were reported as premature (6.2%). Average maternal age at first birth was 23.5 (SD 4.4), and mean number of live births was 3.0 (SD 1.5).

Women who delivered a low birth weight infant (<2500 g.) were significantly more likely to be black and to have a lower family income compared to women who delivered a normal weight infant (>=2500 g., Table 6). They were also more likely to smoke at some point during their lifetimes, to have been younger than age 20 at the time of their first births, and, as expected, were more likely to deliver preterm compared to women who delivered a normal weight infant. Women who delivered a low birth weight infant were also more likely to be taking anti-hypertensive medication at the baseline visit (mean age 73) compared to women who delivered a normal weight first birth.

In unadjusted analyses of cardiovascular risk factors measured continuously, systolic blood pressure showed an inverse association with infant birth weight (r=-0.151, p-value=0.001). Diastolic blood pressure showed a similar but weaker association (r=-0.095, p-value=0.041). Weight at each of three intervals across a woman's life time was positively correlated with infant birth weight, with correlation coefficients ranging from 0.091 (p-value=0.052) at age 25 to 0.123 (p-value=0.006) at the baseline visit. None of the metabolic measures were linearly associated with infant birth weight. CRP was the only inflammatory marker that was significantly (and inversely) associated with infant birth weight (r=-0.096, p-value=0.041).

After adjustment for race and age (Table 7), women who delivered a LBW infant had the lowest average BMI at baseline when compared to women with a normal weight infant (26.6 kg/m^2 vs. 28.0 kg/m^2; p=0.057, but the highest abdominal circumference (98.1 cm v. 95.0 cm; p-value=0.007). Visceral fat was also higher in this group compared to women with normal weight first births (p-value=0.076).

Women with a prior LBW baby had significantly higher levels of IL-6 compared to women with normal weight infants after adjustment for race, age and BMI (p-value=0.021, Table 8). CRP demonstrated a similar but weaker trend (p-value=0.059). Systolic blood pressure was elevated in this group of women (p-value=0.048), and pulse pressure was marginally elevated (p-value=0.069). For women who delivered LBW versus normal, fasting insulin (p-value=0.064) and triglycerides (p-value=0.071) were marginally elevated and these women were more insulin resistant (p-value=0.045). These results did not change when current smokers (n=37) were excluded. Additional adjustment for lifetime cigarette exposure measured in pack years had no substantial effect on most estimates with the exception that it attenuated the results for the inflammatory markers, but IL-6 (0.794 pg/ml(log) vs. 0.602 pg/ml(log); p-value=0.043) and

CRP (0.887 µg/ml(log) vs. 0.706µg/ml(log); p-value=0.157) remained significantly or marginally elevated in women who delivered a LBW infant when compared to women with a normal weight infant.

Considering separately white (n=249) and black women (n=195), those in both groups with LBW infants had higher waist circumferences and elevations in systolic blood pressure, triglycerides, IL-6, and CRP compared to women with normal weight infants. The one race-specific finding related to fasting insulin. There was no difference in fasting insulin among black women who delivered LBW infants when compared to black women with normal weight infants (2.17 IU/ml (log) vs 2.11 IU/ml (log); p-value=0.567), and yet fasting insulin was significantly elevated in white women with a LBW versus normal birth weight infant (2.10 IU/ml(log) vs. 1.83 IU/ml (log); p-value=0.016).

Despite small numbers (n=18), the sub-group of women who delivered an infant that was both preterm and LBW had, on average, the smallest babies and the greatest lifetime cigarette smoking exposure (Table 9). They also had the highest waist circumferences, the highest systolic blood pressures and pulse pressures, and the highest levels of CRP, insulin resistance, and hemoglobin A1c. These elevations were significant or marginally significant when compared to women with normal weight first births.

3.5. DISCUSSION

Among this group of older women, infant birth weight was inversely related to certain inflammatory, metabolic and vascular markers independent of age, race, BMI, and lifetime exposure to cigarette smoking. These associations were present in women up to 60 years post

partum. These data support a small but emerging body of evidence that LBW pregnancies, in particular those complicated by growth restriction or preterm delivery, may involve pathways that lead to poor pregnancy outcomes during the reproductive years and higher cardiovascular risk later in life.

Our findings are consistent with those from the only two comparable studies that related cardiovascular risk factors to reproductive history. Fifty years after a LBW first pregnancy, Lawlor, et al, reported that systolic blood pressure was elevated and insulin resistance was more common. [6] Walker, et al, also reported an inverse association between maternal systolic blood pressure and infant birth weight 19 years after delivery.[5]

Maternal pre-pregnancy BMI is positively correlated with infant birth weight [29-31], and as expected, small women in our study had smaller babies. However, our results suggest that women who delivered a LBW infant had a distinct body composition in older adulthood, with low BMI, high waist circumference, and high visceral fat. The concept of a 'metabolically obese, normal weight' individual has been described as an individual with a relative preponderance of visceral fat, modest overall weight gain, insulin resistance and greater risk for type 2 diabetes.[32-34] Women who deliver a LBW infant could be at higher risk to develop these attributes. We were unable to determine if these women had higher waist circumferences prior to their first birth, although there is evidence that pre-pregnancy waist-hip ratio is positively correlated with infant birth weight [30] suggesting that abdominal adiposity in these women with small babies may occur post partum. Interestingly, women in our study with a LBW infant did not have higher rates of diabetes.

Women in our study who delivered a LBW infant were more likely to be on anti-hypertensive medications, to have higher systolic blood pressures, and to have higher pulse

pressures than women who delivered normal weight infants. Previous studies have shown that women with elevated blood pressure before or during pregnancy, without superimposed preeclampsia, have smaller babies and an elevated risk for preterm delivery.[22-24] In addition, small blood pressure elevations during pregnancy in women who remain normotensive have been shown to restrict fetal growth.[35] These results suggest that occult vascular disease could lead to pregnancies complicated by placental insufficiency, resulting in restricted fetal growth or preterm delivery [22, 36-40], and manifesting later in life as hypertension.

Inflammatory markers IL-6 and CRP were also elevated in women with a LBW infant, suggesting that these women may be predisposed to up-regulation of inflammation that has been associated with growth restricted pregnancies [41, 42] and increased CVD risk.[43, 44] Alternatively, or additionally, elevated inflammatory markers could reflect the increased central adiposity and visceral fat accumulated in these women as they age.[45, 46]

Women in our study who delivered a LBW infant had higher levels of fasting insulin than women with normal or high birth weight infants, they were more insulin resistant, but not more likely to be diabetic. These findings exactly replicate the Lawlor study. [6] While visceral fat, independent of BMI, is a particularly strong marker of insulin resistance in middle-aged[47, 48] and elderly adults[49], it may have developed later in adulthood among women with a LBW delivery. This suggestion derives from the observation that diabetes mellitus prior to pregnancy does not result in LBW babies [31]. Furthermore, the presence of insulin resistance without diabetes mellitus may reflect a recent pathophysiology which has not progressed.

There are several strengths to our study. The strong representation of black women in the Health ABC cohort made it an ideal population to study, as the rates of LBW and CVD among

black women are almost twice that of white women.[50, 51] In addition, we were able to investigate a variety of cardiovascular risks, and had extensive data on body composition.

Our study also has limitations. Because pregnancy history data were collected via recall, our results may be imprecise. Mothers have been found to reliably recall certain pregnancy characteristics. One study confirmed the validity of maternal recall of infant birth weight, preterm status, and cigarette smoking when compared to hospital records reflecting actual events that occurred, on average, 32 years after delivery.[52] While it has been demonstrated that women recall birth weight with an average underestimate of 25 to 95 g [25, 52, 53], recall is most precise for small babies and first births.[25] That several characteristics of women in our study who delivered a LBW infant were consistent with well known attributes associated with this outcome (low socioeconomic status, black race, higher rates of smoking, and young maternal age) is reassuring. Nonetheless, assuming the presence of misclassification, it is unlikely that women would over or under report infant birth weight systematically based on CVD risk so the impact of recall bias would likely be that our observed associations were attenuated.

Community dwelling, well-functioning women who survive to age 80 with reasonable cognitive function are healthier than the general population, thus limiting the generalizability, but not the validity, of our findings. Previous studies identified an association between infant birth weight and maternal cardiovascular death in relatively young women. Preexisting CVD was not an exclusion criterion for participation in our study, but the impact of survival bias would be to underestimate the true magnitude of an effect.

Our ability to distinguish between preterm and growth restricted LBW infants was limited. Our results suggest that delivery of small, preterm babies is associated with a higher

maternal cardiovascular risk prognosis, as was found in one other study.[3] This requires further investigation in a population where gestational age can be precisely characterized.

Our results confirm that older women who delivered a first pregnancy complicated by LBW had elevations in systolic blood pressure, pulse pressure, IL-6, CRP, and fasting insulin compared to women with normal weight infants. They also had the lowest BMI compared to women who delivered normal or high birth weight infants, but the highest abdominal circumference and visceral fat content. Our study provides epidemiologic evidence of an inverse association between infant birth weight and maternal risk for cardiovascular disease. These findings need to be replicated and extended, but raise the possibility that sub-clinical maternal chronic disease risk may contribute to the persistent public health challenges of LBW and preterm delivery. LBW may mark women who could benefit from screening and intervention to delay onset of cardiovascular disease.

Table 6: Maternal Characteristics (% or mean +-SE) according to birth weight of first birth

		Low birth weight (<2500) (n=56)	p Value*	Normal birth weight (>=2500) (n=390)
Age at Baseline		73.3 ± 0.3	0.477	73.0 ± 0.1
Black		62.5%	0.003	41.3%
Education				
	Less than high school	12.5%	0.760	15.4%
	High school graduate	46.4%		48.0%
	Postsecondary	41.1%		36.7%
Family income				
	Less than $10,000	18.9%	0.070	12.1%
	$10,000 to $25,000	52.8%		42.1%
	$25,000 to $50,000	17.0%		34.2%
	$50,000+	11.3%		11.5%
Smoking				
	Never	46.4%	0.218	57.7%
	Former	41.1%		34.6%
	Current	12.5%		7.7%
Pack years smoking		19.6 ± 3.5	0.036	12.6 ±1.1
Smoked during pregnancy		29.1%	0.185	21.2%
Age at first birth		22.5 ± 0.6	0.065	23.6 ± 0.2
Younger than 20 at first birth		30.4%	0.010	16.2%
Premature delivery (<37 weeks)		32.1%	<.0001	2.3%
Diabetes mellitus		9.1%	0.969	9.3%
Antihypertensives		64.3%	0.061	50.9%
Statins		19.6%	0.908	20.3%
* Chi square or t tests				

Table 7: Comparison of maternal body composition characteristics according to infant birth weight groups, adjusted for race and age

	<2500 (n=56)	**p Value***	**2500-3500 (n=293)**	**>3500 (n=97)**	**p Value***
Weight (kg)	66.2	0.047	70.2	75.2	0.002
Height (mm)	1577.7	0.656	1581.8	1598.3	0.022
BMI, age 25 (kg/m²)	21.8	0.771	22.0	22.1	0.757
BMI, age 50 (kg/m²)	24.5	0.117	25.3	26.0	0.108
BMI, study baseline (kg/m²)	26.62	0.057	28.01	29.4	0.021
Abdominal circumference (cm) **	98.1	0.007	95.0	96.4	0.138
Visceral fat (cm²) **	121.9	0.076	110.4	110.0	0.980
Abdominal subcutaneous fat (cm²) **	345.2	0.764	342.5	344.0	0.834
Total percent fat **	39.8	0.699	40.0	39.9	0.791
*Compared to normal birth weight group (2500 g - 3500 g)					
**Adjusted for BMI, race and age at baseline					
Excludes pregnancies complicated by hypertension or preeclampsia					

Table 8: Comparison of selected maternal characteristics according to delivery of a low birth weight (<2500 g.) vs. normal weight (>=2500 g.) infant, adjusted for race, age and BMI

		Low birth weight <2500 (n=56)	p Value	Normal birth weight >=2500 (n=390)
Lipids				
	Total cholesterol (mg/dl)	218.5	0.618	220.3
	HDL (mg/dl)	61.3	0.611	60.2
	LDL (mg/dl)	128.1	0.726	129.9
	Triglycerides (mg/dl)	142.0	0.071	126.7
Vascular				
	Systolic blood pressure	143.1	0.048	137.3
	Diastolic blood pressure	73.5	0.359	72.2
	Pulse pressure	69.7	0.069	65.1
	Pulse wave velocity (cm/sec)	780.6	0.854	772.8
Metabolic				
	Fasting glucose (mg/dl)	99.2	0.723	97.9
	Fasting insulin (IU/ml) *	8.1	0.064	7.1
	Insulin resistance (HOMA score) *	1.9	0.045	1.6
	Hemoglobin A1C	6.3	0.881	6.2
Inflammatory				
	IL-6 (pg/ml)	2.3	0.021	1.8
	TNF-α (pg/ml)	3.0	0.194	3.3
	CRP (μg/ml)	2.5	0.059	2.0
* Non-diabetics Excludes pregnancies complicated by hypertension or preeclampsia				

Table 9: Selected maternal characteristics according to preterm delivery status and infant birth weight, adjusted for race, BMI and age

	Infant preterm and LBW (<37 weeks, <2500 g) (n=18)	p Value*	Infant LBW but not preterm (>37 weeks, <2500 g) (n=38)	p Value*	Normal (>=2500 g) (n=390)
Infant birth weight	1787		2282		3258
Pack years smoking**	25.4	0.022	16.8	0.297	12.7
BMI	26.4	0.115	26.7	0.057	28.3
Waist circumference	99.6	0.026	97.5	0.114	95.3
Visceral fat	107.88	0.796	129.28	0.014	110.39
Systolic blood pressure	146.87	0.057	141.51	0.235	137.26
Pulse pressure	72.36	0.086	68.41	0.263	65.08
IL-6 (pg/ml)	2.30	0.124	2.24	0.062	1.82
CRP (μg/ml)	4.01	0.076	2.33	0.243	1.96
Fasting insulin (IU/ml)	8.24	0.203	8.04	0.141	7.07
Insulin resistance (HOMA)	1.97	0.112	1.84	0.150	1.60
Hemoglobin A1C	6.59	0.075	6.09	0.314	6.23
Triglycerides (mg/dl)	128.5	0.893	148.9	0.031	126.7

* Compared to normal birth weight group (>=2500 g)
**Unadjusted
Excludes pregnancies complicated by hypertension or preeclampsia

3.6. LITERATURE CITED

1. Davey Smith, G., S. Harding, and M. Rosato, *Relation between infants' birth weight and mothers' mortality: prospective observational study.* BMJ, 2000. **320**(7238): p. 839-40.
2. Smith, G., J. Pell, and D. Walsh, *Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births.* Lancet, 2001. **357**(9273): p. 2002-6.
3. Davey Smith, G., et al., *Birth dimensions of offspring, premature birth, and the mortality of mothers.* Lancet, 2000. **356**: p. 2066-67.
4. Irgens, H., et al., *Long term mortality of mothers and fathers after pre-eclampsia: population based cohort.* BMJ, 2001. **323**(7323): p. 1213-17.
5. Walker, B., et al., *Contribution of parental blood pressures to association between low birth weight and adult high blood pressure: cross sectional study.* BMJ, 1998. **316**: p. 834-7.
6. Lawlor, D., G. Davey Smith, and S. Ebrahim, *Birth weight of offspring and insulin resistance in late adulthood: cross sectional survey.* BMJ, 2002. **325**: p. 359-62.
7. David, R. and J. Collins, *Differing birth weight among infants of U.S.-born Blacks, African-born Blacks and U.S.-born Whites.* NEJM, 1997. **337**(17): p. 1209-1214.
8. Collins, J. and R. David, *The differential effect of traditional risk factors on infant birthweight among Blacks and Whites in Chicago.* Am J Public Health, 1990. **80**: p. 679-81.
9. Abrams, B. and V. Newman, *Small-for-gestational age birth: maternal predictors and comparison with risk factors of spontaneous delivery in the same cohort.* Am J Obstet Gynecol, 1991. **164**: p. 785-90.
10. Shiono, P. and M. Klebanoff, *Ethnic differences in preterm and very preterm delivery.* Am J Public Health, 1986. **76**(11): p. 1317-21.
11. Abrams, B., et al., *Maternal weight gain and preterm delivery.* Obstetrics and Gynecology, 1989. **74**: p. 577-83.
12. Goldenberg, R., J. Iams, and B. Mercer, *The preterm prediction study: the value of new vs. standard risk factors.* American Journal of Public Health, 1998. **88**(2): p. 233-8.
13. Zeitlin, J., et al., *Are risk factors the same for small for gestational age versus other preterm births.* Am J Obstet Gynecol, 2001. **185**(1): p. 208-15.
14. Fox, S., T. Koepsell, and J. Daling, *Birth weight and smoking during pregnancy-effect modification by maternal age.* Am J Epidemiol, 1994. **139**: p. 1008-15.
15. Fang, J., S. Madhavan, and M. Alderman, *The influence of maternal hypertension on low birth weight: differences among ethnic populations.* Ethnicity and Disease, 1999. **9**(369-76).
16. Sattar, I. and I. Greer, *Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening?* BMJ, 2002. **325**: p. 157-160.
17. Visser, M., et al., *Leg muscle mass and composition in relation to lower extremity performance in men and women aged 70 to 79: the Health, Aging and Body Composition Study.* JAGS, 2002. **50**(5): p. 897-904.

18. Rooks, R., et al., *The association of race and socioeconomic status with cardiovascular disease indicators among older adults in the Health, Aging, and Body Composition Study.* Journal of Gerontology: Social Sciences, 2002. **57B**(4): p. S247-S256.
19. Roberts, J. and K. Lain, *Recent insights into the pathogenesis of pre-eclampsia.* Placenta, 2002. **23**: p. 359-372.
20. Chesley, L., J. Annitto, and R. Cosgrove, *The remote prognosis of eclamptic women: sixth periodic report.* Am J Obstet Gynecol, 1976. **124**: p. 446-59.
21. Sibai, B., A. El-Nazer, and A. Gonzalez-Ruiz, *Severe preeclampsia in young primigravid women: subsequent pregnancy outcome and remote prognosis.* Am J Obstet Gynecol, 1986. **155**: p. 1011-6.
22. Ananth, C., A. Peedicayil, and D. Savitz, *Effect of hyptertensive diseases in pregnancy on birthweight, gestational duration, and small-for-gestational age births.* Epidemiology, 1995. **6**: p. 391-395.
23. Haelterman, E., et al., *Effect of uncomplicated chronic hypertension on the risk of small-for-gestational age birth.* American Journal of Epidemiology, 1997. **145**(8): p. 689-695.
24. Waugh, J., et al., *Birth weight and 24-hour ambulatory blood pressure in nonproteinuric hypertensive pregnancy.* Am J Obstet Gynecol, 2000. **183**(3): p. 633-637.
25. Seidman, D., et al., *Accuracy of mothers' recall of birthweight and gestational age.* British Journal of Obstetrics and Gynaecology, 1987. **94**(8): p. 731-5.
26. Fried, L., et al., *The Cardiovascular Health Study: design and rationale.* Annals of Epidmiology, 1991. **1**(3): p. 263-276.
27. Matthews, D., et al., *Homeostasis model assessment: insuline resistance and beta-cell function from fasting glucose and insulin concentrations in man.* Diabetologia, 1985. **28**: p. 412-19.
28. Niewenweg, R., et al., *Adult height corrected for shrinking and secular trend.* Annals of Human Biology, 2003. **30**(5): p. 563-569.
29. Goldenberg, R., et al., *Maternal risk factors and their influence on fetal anthropotetric measurements.* Am J Obstet Gynecol, 1993. **168**: p. 1197-1205.
30. Brown, J., et al., *Maternal waist-to-hip ratio as a predictor of newborn size; results of the Diana Project.* Epidemiology, 1995. **7**(1): p. 62-66.
31. Green, J., et al., *Influence of maternal body habitus and glucose tolerance on birth weight.* Obstetrics and Gynecology, 1991. **78**(2): p. 235-239.
32. Dvorak, D., et al., *Phenotypic characteristics associated with insulin resistance in metabolically obese but normal-weight young women.* Diabetes, 1999. **48**: p. 2210-2214.
33. Ruderman, N., S. Schneider, and P. Berchtold, *The "metabolically-obese," normal-weight individual.* Am J Clin Nutr, 1981. **34**: p. 1617-21.
34. Goodpaster, B., et al., *Association between regional adipose tissue distribution and both type 2 diabetes and impaired glucose tolerance in elderly men and women.* Diabetes Care, 2003. **26**(2): p. 372-379.
35. Churchill, D., I. Perry, and M. Beevers, *Ambulatory blood pressure in pregnancy and fetal growth.* Lancet, 1997. **349**: p. 7-10.
36. Salafia, C., et al., *Intrauterine growth restriction in infants of less than thirty-two weeks' gestation: associated placental pathologic features.* Am J Obstet Gynecol, 1995. **173**: p. 1049-57.

37. Sheppard, B. and J. Bonnar, *The ultrastructure of the arterial supply of the human placenta in pregnancy complicated by fetal growth restriction.* Br J Obstet Gynaecol, 1976. **83**: p. 948-59.
38. Pijnenborg, R., *The placental bed.* Hypertens Pregnancy, 1996. **15**: p. 7-23.
39. Khong, T., et al., *Inadequate maternal vascular response to placentation in pregnancies complicated by small-for-gestational age infants.* Br J Obstet Gynaecol, 1986. **93**: p. 1049-59.
40. Kim, Y., et al., *Failure of physiologic transformation of the spiral arteries in patients with preterm labor and intact membranes.* Am J Obstet Gynecol, 2003. **189**(4): p. 1063-1069.
41. Bartha, J., R. Romero-Carmona, and R. Comino-Delgado, *Inflammatory cytokines in intrauterine growth retardation.* Acta Obstet Gynecol Scand, 2003. **82**: p. 1099-102.
42. Silver, R., B. Schwinzer, and J. McGregor, *Interleukin-6 levels in amniotic fluid in normal and abnormal pregnancies: preeclampsia, small for gestational age fetuses, and preterm labor.* Am J Obstet Gynecol, 1993. **169**(5): p. 1101-5.
43. Ridker, P., et al., *C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women.* NEJM, 2000. **342**(12): p. 836-43.
44. Tracy, R., et al., *Relationship of C-Reactive Protein to Risk of Cardiovascular Disease in the Elderly.* Arteriosclerosis, Thrombosis, and Vascular Biology, 1997. **17**(6): p. 1121-1127.
45. Tracy, R., *Is visceral adiposity the "enemy within"?* Arteriosclerosis, Thrombosis, and Vascular Biology, 2001. **21**: p. 881-883.
46. Yudkin, J., et al., *C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue?* Arteriosclerosis, Thrombosis, and Vascular Biology, 1999. **19**: p. 972-978.
47. Despres, J.-P., *Abdominal obesity as important component of insulin resistance syndrome.* Nutrition, 1993. **9**(452-459).
48. Ross, R., L. Fortier, and R. Hudson, *Separate associations between visceral and subcutaneous adipose tissue distribution, insulin and glucose levels in obese women.* Diabetes Care, 1996. **19**: p. 1404-11.
49. Kohrt, W., et al., *Insulin resistance in aging is related to abdominal obesity.* Diabetes, 1993. **42**: p. 273-281.
50. National Center for Health Statistics, *Health, United States*. 2003.
51. Mosca, L., et al., *Cardiovascular disease in women: a statement for healthcare professionals from the American Heart Association.* Circulation, 1997. **96**(7): p. 2468-82.
52. Tomeo, C., et al., *Reproducibility and validity of maternal recall of pregnancy-related events.* Epidemiology, 1999. **10**(6): p. 774-7.
53. Olson, J., et al., *Medical record validation of maternally reported birth characteristics and pregnancy-related events: a report from the Children's Cancer Group.* Am J Epidemiol, 1997. **145**(1): p. 58-67.

4. ARTICLE THREE: LOW BIRTH WEIGHT, PRETERM DELIVERY AND REMOTE MATERNAL CARDIOVASCULAR RISK: THE HEALTH, AGING AND BODY COMPOSITION STUDY

4.1. ABSTRACT

Women who have borne a low birth weight or preterm baby may be at elevated risk for later cardiovascular disease. In a cross sectional study of older women we investigated whether delivery of a low birth weight (<2500 g) or preterm (<37 weeks gestation) infant increased maternal risk for subclinical or clinical cardiovascular disease. Participants were 446 women (mean age 80 years; 47% black) enrolled in the Pittsburgh, PA field center of The Health, Aging and Body Composition Study. Women reported birth weight, smoking status, prematurity, and selected complications for each pregnancy. Analysis was limited to first births not complicated by hypertension or preeclampsia. After an average follow up of 57 years, women who had delivered a low birth weight or preterm infant had a marginally increased risk for clinical cardiovascular disease. After adjustment for well known cardiovascular risk factors, including vascular, demographic and lifestyle covariates, women who delivered a preterm infant had a 2.77-fold increase (95% CI 1.06-7.24) in risk for clinical cardiovascular disease, compared to women with infants born on time. Women who delivered infants that were both early and small demonstrated a 4.21-fold increase in risk (95% CI 1.23-14.45). The increased risk appeared to be in women with hypertension suggesting that vascular disease could moderate the relationship between infant birth characteristics and maternal cardiovascular disease. These results need to be replicated and expanded, but support an emerging body of evidence that many years after having had a small baby, women are at elevated risk for cardiovascular disease.

4.2. INTRODUCTION

Women who have borne a low birth weight or preterm baby may be at elevated risk for later cardiovascular disease. Large registry-based observational studies found that a low birth weight (LBW) delivery increased maternal risk for cardiovascular death 7 to 11-fold [1, 2] and that risk for cardiovascular death was 2 to 3 times higher for women who delivered a preterm infant compared to those who delivered an infant at term. [3, 4] In the few studies to relate infant birth weight to later maternal cardiovascular risk factors, bearing a low birth weight infant was inversely related to maternal systolic blood pressure [5, 6] and insulin resistance [6], but had no association with maternal lipid levels. [6, 7]

Underlying risk for cardiovascular disease may affect a woman's ability to successfully adapt to the vascular or metabolic demands of pregnancy, leading to poor pregnancy outcomes during the reproductive years and higher cardiovascular risk later in life. [8] There is evidence that even small elevations in maternal blood pressure during pregnancy that remain within the 'normal' range can restrict fetal growth [9], and placental vascular lesions have been associated with fetal growth restriction [10] and preterm delivery. [11] In addition, infection or inflammation has been implicated in preterm birth [11-13], fetal growth restriction [13, 14], as well as cardiovascular disease risk among women. [15]

In a cross sectional study of older women we investigated the relationship between recalled pregnancy characteristics and cardiovascular disease status. Specifically, we examined whether women who reported they had borne small (< 2500 g) or preterm (< 37 weeks gestation) infants had an increased risk for clinical or subclinical cardiovascular disease. We also sought to

assess whether vascular, metabolic, body composition or inflammatory measures may mediate this risk.

4.3. METHODS

4.3.1. Participants

The Health, Aging and Body Composition (Health ABC) Study is a large on-going epidemiologic study of how changes in body composition affect morbidity, disability, and mortality. A total of 3,075 community dwelling participants (50% female) were enrolled in Pittsburgh, Pennsylvania and Memphis, Tennessee in 1997-1998. Recruitment procedures have been described elsewhere in detail.[16] All participants signed an informed consent approved by the institutional review board at the University of Pittsburgh. Eligibility criteria included: age 70 to 79; self-report of no difficulty walking one quarter mile or climbing 10 steps without resting; no difficulty performing basic activities of daily living; no use of assistive devices to ambulate; no history of active treatment for cancer in the prior three years; and no plans to move out of the area in the next three years. Based on these criteria participants were considered well functioning.[17]

Among 608 women in the Pittsburgh cohort who were interviewed in 2003 and 2004 as part of the year 7 follow-up visit, we included questions about pregnancy history. 597 women (98%) provided pregnancy history details. Of the 507 (85%) women who had at least one live birth, 466 (92%) provided their first born's birth weight. Mean age at this interview was 80, and 47% of women were black. We excluded women who reported hypertension during pregnancy

(n=11) or preeclampsia (n=11) to describe maternal prognosis after delivery of a LBW infant beyond the well known increase in cardiovascular risk for women with these pregnancy complications. [18-23] Our analysis was based on the recalled birth characteristics of 446 women and their updated cardiovascular disease status (prevalent and incident) at year 7 of follow up.

4.3.2. Recalled birth characteristics

Women were asked to report the birth weight for each pregnancy lasting more than six months. Smoking status, prematurity (early vs. on time and in weeks) as well as selected complications (hypertension during pregnancy and preeclampsia) were also assessed for each pregnancy. Analysis was limited to first births, as birth weight and gestational age are recalled more accurately for first births compared to subsequent births.[24]

Infant birth weight was converted to grams for the purposes of the analysis, and was evaluated as a continuous variable and a dichotomous low birth weight variable (<2500 g vs. >=2500 g). Infants reported as being born early (< 37 weeks gestation) were considered preterm. LBW was stratified by preterm delivery to identify a subset of deliveries that were small and premature.

4.3.3. Cardiovascular disease endpoints

We categorized participants into three cardiovascular disease groups: those with clinical cardiovascular disease, those with subclinical cardiovascular disease, and those with no clinical or subclinical cardiovascular disease.

Participants with clinical cardiovascular disease included those with prevalent disease and those with incident events. Prevalent cardiovascular disease was ascertained at baseline (1997 to 1998) via self-report and was validated with algorithms that included selected medications and ECG results. These disease algorithms were developed by the Health ABC investigators to mirror the adjudicated diagnoses in the Cardiovascular Health Study. [25] There were 101 participants with the following prevalent conditions: myocardial infarction, angina, coronary artery bypass surgery, or percutaneous transluminal angioplasty (70 participants); ECG evidence of myocardial infarction (3 participants); stroke (22 participants); or peripheral vascular disease (6 participants). Incident events that occurred after baseline were ascertained by phone contact or at the clinic examination every six months (1998 to 2002), validated by medical record review, and adjudicated by committee. [26] Among 31 participants with incident cardiovascular events, 30 had a myocardial infarction or angina and 1 had a stroke. Overall, 132 women (29.6%) were identified with clinical cardiovascular disease.

Participants with prevalent subclinical cardiovascular disease were categorized according to previously published protocol [27-29] on the basis of a finding of one of the following assessed at baseline: positive results on the Rose questionnaire for angina (9 participants); intermittent claudication (10 participants); an ankle-brachial index <0.9 (15 participants); or the

presence of electrocardiographic abnormalities (70 participants). Ankle-brachial index was the ratio of the mean of two resting measurements of systolic blood pressure in the right arm and both legs using an 8-MHz Doppler stethoscope. The lowest ankle-brachial index of either leg was used. Electrocardiographic abnormalities were detected by a 12-lead electrocardiogram using a standardized protocol, and all data were acquired using the Marquette Electronic MAC PC Resting ECG Analysis System (Marquette Electronics Inc., Milwaukee, Wisconsin). Clinical physicians examined all abnormal cardiograms, and all ECG data were transmitted daily to the core electrocardiographic lab, where the quality of the ECG was assessed and the interpretation confirmed. ECG abnormalities considered as evidence of subclinical disease included: atrial fibrillation; long PR interval; short PR interval; ST- or T-wave abnormalities; left bundle branch block; right bundle branch block; intraventricular block; left anterior hemiblock; left anterior hemiblock with right bundle branch block; and incomplete left bundle branch block. Overall, 104 women (23.3%) were categorized as having subclinical cardiovascular disease.

The remaining 210 participants (47.1%) without evidence of clinical or subclinical cardiovascular disease comprised the group with no cardiovascular disease.

4.3.4. Covariates

Covariates included characteristics with an established association with LBW or cardiovascular disease. Sociodemographic and lifestyle variables included age, race, education, income, and smoking status (characterized as never, former, current; and measured in pack years [the average packs of cigarettes smoked daily multiplied by years smoking]). Participants reported annual family income at study baseline, and also described how well their income fit

their needs (poorly, fairly well, very well). Due to the high number of missing values for family income (n=63, 14%), a low socioeconomic indicator variable was calculated for women who reported either the lowest quartile of family income or the lowest level of income adequacy.

Dichotomous disease covariates included adjudicated presence of diabetes mellitus (self-report and medication), hypertension (self report and medication, or systolic blood pressure above 135 and diastolic blood pressure above 85), and metabolic syndrome (NCEP III definition [30] as three or more of the following: abdominal circumference > 88; blood pressure >=130/85 or taking anti-hypertensive medication; fasting glucose >= 110 or taking insulin or oral antidiabetic agents; HDL cholesterol < 50; or triglycerides >= 150). Body composition covariates included BMI (kg/m²), abdominal circumference, and visceral fat (estimated with CT scans between fourth and fifth lumbar vertebrae).

Additional covariates included: systolic and diastolic blood pressures measured according to standard protocol [25]; pulse pressures (systolic minus diastolic blood pressure); pulse wave velocity (measured from simultaneous Doppler flow signals obtained from the right carotid and right femoral arteries by use of nondirectional transcutaneous Doppler flow probes); total cholesterol, high-density lipoprotein cholesterol, and triglycerides (all measured on fasting serum by a colorimetric technique on a Johnson and Johnson Vitros 950 analyzer, New Brunswick, NJ); serum insulin (non-diabetics only) and glucose (determined using a radioimmunoassay kit [Pharmacia, Uppsala, Sweden]; insulin resistance (estimated with the homeostasis model assessment: the product of fasting glucose and insulin concentrations in mmol/l divided by 22.5) [31]; low-density lipoprotein cholesterol (estimated with the Fiedwald equation); hemoglobin A1c (via ion-exchange high performance liquid chromatography (Biorad Variant analyzer); and

IL-6 and CRP (measured in duplicate from overnight fasting serum by an enzyme-linked immunosorbent essay kit from R&D Systems [Minneapolis, MN]).

4.3.5. Statistical analysis

Differences in means and proportions of covariates were assessed across the three cardiovascular disease groups using analysis of variance and chi square tests. Analysis of covariance was used to detect more precise differences in means for body composition variables (adjusted for race and age) and vascular, metabolic and inflammatory measures (adjusted for race, age and BMI). Inflammatory markers, triglycerides, glucose, insulin, hemoglobin A1c, and aPWV were log-transformed for the purposes of analysis as they were not normally distributed, but results are presented as actual values. Simple logistic regression was used to assess the association between a woman's subclinical or clinical cardiovascular disease risk and infant characteristics: birth weight (as a continuous variable measured in kilograms), LBW, preterm status, and the combined effect of delivering an infant both LBW and preterm. The referent group was women with no cardiovascular disease. Multivariate logistic regression models were built to assess the independent association between infant characteristics and clinical cardiovascular disease, as there were no univariate associations between any birth outcomes and subclinical cardiovascular disease. The models were adjusted for age, race, low socioeconomic status, young maternal age, and the lipid covariates (HDL cholesterol and use of statins) that had a univariate relationship with clinical cardiovascular disease, as maternal lipid levels did not differ based on infant birth weight. These adjusted models were then separately adjusted for body composition (BMI, visceral fat, abdominal circumference), inflammatory (IL-6 and CRP),

vascular (systolic and diastolic blood pressures, PWV, hypertension), and metabolic (glucose, triglycerides, diabetes) covariates to identify pathways that may moderate or mediate an association between infant birth weight, prematurity and cardiovascular disease. Tests for interaction were done if risk estimates appeared to be altered. All tests were two-sided, and differences with a p-value <0.05 were considered significant; differences with a p-value <0.1 were considered marginally significant.

4.4. RESULTS

Among the 446 women who recalled the birth weight of their first born, mean birth weight was 3117 g (SD 582), and 56 (12.6%) women reported having a baby of birth weight less than 2500 g. Thirty first births were reported as premature (6.2%); 18 of these were also LBW. Average maternal age at first birth was 23.5 (SD 4.4), and mean number of live births was 3.0 (SD 1.5).

Women with subclinical and clinical cardiovascular disease were marginally older than women free from disease (Table 10). Women with clinical cardiovascular disease were more likely to be black and somewhat more likely to report low socioeconomic status compared to women with no disease. Women with subclinical cardiovascular disease had higher levels of education and were less likely to be of low socioeconomic status compared to women with no disease. Women with subclinical cardiovascular disease were combined with the group with no disease for subsequent analysis, as the two groups had similar rates of LBW and premature deliveries.

Women with clinical cardiovascular disease vs. none (no disease and subclinical, n=314) were more likely to have diabetes mellitus (p=0.001), to have lower levels of HDL (p-value=0.044), and to have higher levels of fasting glucose (p=0.006, Table 11). Women with clinical cardiovascular disease were more also more likely to use anti-hypertensive medication (p<0.0001) and statins (p=0.002) compared to women with no cardiovascular disease, and they were somehwhat more likely to have hypertension. The two groups of women had similar BMIs, but the group with clinical cardiovascular disease had somewhat elevated levels of visceral fat, although this difference was not significant.

Women with clinical cardiovascular disease vs. none were more likely to have been younger than age 20 at the time of their first births (p=0.012), and they had moderately higher rates of low birth weight (p=0.089) or preterm delivery (p=0.081).

Delivery of a low birth weight vs. normal weight infant was associated with a modestly increased risk for clinical cardiovascular disease (OR 1.63, 95% CI 0.87 to 3.05, Table 12). Delivery of a preterm vs. term infant produced an unadjusted risk for clinical cardiovascular disease of 1.65 (95% CI 0.72 to 3.79) and delivery of an infant both LBW and preterm produced a risk of 2.19 (95% CI 0.79 to 6.04). Risk for cardiovascular disease modestly decreased for each additional kilogram in infant birth weight (OR 0.80, 95% CI 0.56 to 1.15). After adjustment for age, race, young maternal age, low socioeconomic status, HDL cholesterol and use of statins, women who reported that their infant was born premature vs. on time had a modestly elevated 1.93-fold increase in risk of clinical cardiovascular disease (95% CI .79 to 4.72). Risk for cardiovascular disease was 2.50 times higher (95% CI .83 to 7.55) for women with infants that were both small and early compared to women with normal weight infants born on time.

After additional adjustment for the vascular covariates (hypertension, pulse wave velocity, and systolic blood pressure), women who had delivered preterm infants had a statistically significant 2.77-fold increase in risk for cardiovascular disease (95% CI 1.06 to 7.24) when compared to women with term infants (Table 13). Those with babies born both small and early (versus babies born normal weight and on time) had a four-fold increase in risk for clinical cardiovascular disease (OR 4.21 95% CI 1.23 to 14.45). Addition of body composition, inflammatory, and metabolic measures did not appear to alter the risk estimates of infant birth characteristics associated with clinical cardiovascular disease.

The additional adjustment of vascular measures in our model increased the risk estimates for preterm delivery, suggesting interaction. The interaction of preterm delivery and hypertension was not significant (p=0.267), however, likely due to small numbers. When we stratified our adjusted model by presence of hypertension, women with a preterm delivery had a 4.99-fold (95% CI 1.35 to 18.54) increase in clinical cardiovascular disease. In women without hypertension, risk of clinical cardiovascular disease associated with a preterm delivery was reduced to 1.44 (95% CI .23 to 9.00).

4.5. DISCUSSION

Among this group of older women, those who delivered an infant that was LBW or preterm showed an increased risk, albeit marginally significant, of clinical cardiovascular disease. This association was detected with an average follow up of 57 years after delivery and after excluding pregnancies complicated by preeclampsia or hypertension. After adjustment for well known cardiovascular risk factors, including vascular covariates, women who delivered a

preterm infant had a 2.77-fold increase in risk for clinical cardiovascular disease, compared to women with infants born on time. Women who delivered infants that were both early and small demonstrated a 4.21-fold increase in clinical cardiovascular disease risk. The increased risk appeared to be in women with hypertension, suggesting that vascular disease could moderate the relationship between infant birth characteristics and maternal cardiovascular disease. These results support an emerging body of evidence that many years after having had a small baby, women are at elevated risk for cardiovascular disease.

Our study is the first, to our knowledge, to investigate the association between LBW or preterm delivery and maternal cardiovascular morbidity in a population of older women, adjusted for a variety of sociodemographic, physical, and biologic correlates of cardiovascular disease. Large registry-based observational studies, with limited ability to adjust for confounding, found an increased risk for maternal cardiovascular death in relatively young women following a low birth weight [2, 7] or preterm delivery. [3, 4] Our findings among older women are remarkably consistent with the only other study to examine the combined endpoint of maternal cardiovascular hospitalization or death following the delivery of a LBW or preterm infant. Smith, et al, found a 4-fold increase in risk for ischemic heart disease among women who delivered an infant both LBW and preterm 15 to 19 years in the past. [1]

Infant birth weight has been found to be inversely related to maternal systolic blood pressure measured in women aged 34 to 79. [5, 6] Women in our study with clinical cardiovascular disease had high levels of hypertension and elevated pulse wave velocities, a marker of arterial stiffness. When adjusted for both of these factors, women who delivered a preterm infant had almost three times the risk for clinical cardiovascular disease compared to women who delivered infants at term. Although small numbers limited our ability to find

significant interaction, the increased risk of cardiovascular disease associated with preterm delivery was primarily observed in women with hypertension, suggesting that vascular disease may moderate this association.

Previous studies have shown that women with elevated blood pressure before or during pregnancy, without superimposed preeclampsia, have smaller babies and an elevated risk for preterm delivery. [21-23] Even small blood pressure elevations within the 'normal' range in pregnant women who remain normotensive have been shown to be associated with restricted fetal growth. [9, 32] In addition, maternal decidual or myometrial vascular changes have been associated with intrauterine growth restriction [10] and preterm delivery [11] in pregnancies not complicated by preeclampsia or hypertension. These findings suggest that occult maternal vascular disease may contribute to fetal growth restriction and preterm delivery, and over the course of a woman's lifetime could lead to hypertension or arterial stiffness that ultimately increases risk for cardiovascular disease.

We found no association between infant birth weight or preterm delivery and subclinical cardiovascular disease. We may have had limited power to detect what are likely to be more subtle associations. Alternatively, women in our study with subclinical disease may have been healthier or been better clinically managed than those who had progressed to clinical cardiovascular disease by age 80. That they were better educated, had a higher socioeconomic status, and had similar rates of preterm and LBW delivery compared to women with no cardiovascular disease suggests this may be the case.

There are several strengths to our study. The strong representation of black women in the Health ABC cohort made it an ideal population to study, as the rates of LBW [33, 34], preterm delivery [35, 36], and cardiovascular disease [37] among black women are about twice that of

white women. We were able to describe both clinical and subclinical cardiovascular disease, and were able to include extensive physical and biologic covariates associated with LBW, preterm delivery and cardiovascular disease.

Several limitations of our study may affect the interpretation of our results. Our work should be considered preliminary, as many of our estimates were imprecise. Because pregnancy data were collected via recall, our exposure variables are subject to missclassification. Mothers have been found to reliably recall certain pregnancy characteristics. One study confirmed the validity of maternal recall of infant birth weight, preterm status, and cigarette smoking when compared to hospital records reflecting actual events that occurred, on average, 32 years after delivery. [38] While it has been demonstrated that women recall birth weight with an average underestimate of 25 g to 95 g [24, 38, 39], recall is most precise for first births and small babies. [24] Nonetheless, assuming the presence of misclassification, it is unlikely that women would systematically over or under report infant birth weight or preterm status based on cardiovascular disease risk so the impact of recall bias would likely be that our observed associations were attenuated.

Community dwelling, well-functioning women who survive to age 80 with reasonable cognitive function are healthier than the general population, thus limiting the generalizability, but not the validity, of our findings. Preexisting cardiovascular disease was not an exclusion criterion for participation in our study, but the impact of survival bias would be to underestimate the true magnitude of an effect.

Our ability to distinguish between preterm and growth restricted LBW infants was limited. Our results suggest that delivery of small, preterm babies was associated with a higher maternal cardiovascular disease risk, but this should be confirmed in a population where infant

characteristics can be precisely characterized. In addition, we may have underestimated preeclampsia or hypertension during pregnancy due to imprecise maternal recall. Additional studies where these pregnancy complications can be better characterized are needed to validate our findings.

Our results suggest that older women who delivered a small or preterm first birth had an increased risk for clinical cardiovascular disease after adjusting for demographics, smoking, and comorbidities. This was particularly true in women with hypertension or arterial stiffness, suggesting an interaction with maternal vascular disease.

Table 10: Selected maternal characteristics (% or mean and SE) according to cardiovascular disease status

	No CVD (n=210)	Subclinical CVD (n=104)	p Value*	Clinical CVD (n=132)	p Value**
Sociodemographic and Lifestyle					
Age at Baseline	72.8 ± .19	73.3 ± .28	0.159	73.2 ± .24	0.196
Black	37.14%	40.38%	0.578	57.58%	0.000
Education					
Less than high school	16.67%	8.65%	0.046	17.42%	0.932
High school graduate	45.24%	58.65%		43.18%	
Postsecondary	38.10%	32.82%		39.39%	
Low socioeconomic status	14.76%	10.58%	0.305	18.94%	0.310
Ever smoked (former or current)	40.0%	44.2%	0.474	49.2%	0.093
Pack years smoked	11.1 ± 1.5	12.21 ± 2.3	0.688	18.4 ± 2.0	0.005
Pregnancy					
Infant birth weight (g)	3153 ± 40	3103 ± 57	0.479	3071 ± 51	0.213
Low birth weight infant (<2500 g)	10.95%	10.58%	0.920	16.67%	0.128
Premature delivery (<37 weeks)	5.71%	2.88%	0.269	9.09%	0.234
Smoked during pregnancy	20.57%	24.75%	0.405	22.66%	0.651
Age at first birth	23.5 ± .3	23.7 ± .4	0.797	23.4 ± .4	0.746
Younger than age 20 at first birth	15.24%	14.56%	0.875	25.00%	0.025

* Women with subclinical CVD compared to women with no CVD

**Women with clinical CVD compared to women with no CVD

Table 11: Maternal characteristics according to clinical cardiovascular disease vs. none (adjusted for race, age and BMI)

		No CVD (n=314)	Clinical CVD (n=132)	p Value
Body Composition				
	BMI, age 73 (kg/m²)	28.2	28.0	0.805
	Visceral fat (cm²)	110.0	116.1	0.175
Lipids				
	HDL (mg/dl)	61.4	57.9	0.044
	Statins	16.3%	29.6%	0.002
Vascular				
	Hypertension	58.6%	68.2%	0.058
	Antihypertensives	45.1%	70.5%	<.0001
	Systolic blood pressure	138.5	136.9	0.465
	Pulse wave velocity (cm/sec)	757.5	810.8	0.136
Metabolic				
	Fasting glucose (mg/dl)	96.3	102.4	0.006
	Fasting insulin (IU/ml)	7.0	7.65	0.088
	Diabetes mellitus	6.4%	16.0%	0.001
	Metabolic syndrome	39.4%	43.2%	0.461
Inflammatory				
	IL-6 (pg/ml)	1.91	1.79	0.363
	CRP (μg/ml)	2.06	1.94	0.446
Pregnancy				
	Infant birth weight (g)	3079 ± 28	2947 ± 63	0.287
	Low birth weight infant (<2500 g)	10.8%	16.7%	0.089
	Premature delivery (<37 weeks)	4.8%	9.1%	0.081
	Smoked during pregnany	21.9%	22.7%	0.869
	Age at first birth	23.0 ± .2	22.5 ± .4	0.879
	Younger than age 20 at first birth	15.0%	25.0%	0.012

Table 12: Crude and multivariate assessment of clinical cardiovascular disease risk and infant birth characteristics

	Clinical Cardiovascular Disease			
	Crude OR (CI)	p Value	Adjusted OR (CI)*	p Value
Infant birth weight (kg)	0.80 (.56, 1.15)	0.229	.85 (.58-1.24)	0.397
Low birth weight (<2500 g)	1.63 (.87, 3.05)	0.131	1.30 (.66, 2.56)	0.449
Preterm (<37 weeks)	1.65 (.72, 3.79)	0.238	1.93 (.79, 4.72)	0.151
Low birth weight and Preterm**	2.19 (.79, 6.04)	0.131	2.50 (.83, 7.55)	0.104

*Adjusted for age, race, HDL cholesterol, smoking, low SES, maternal age <20, statin use

**Reference group are women with infants normal birth weight (>=2500 g) and not preterm

Table 13: Multivariate assessment of clinical cardiovascular disease risk and infant birth characteristics (adjustment for body composition, inflammatory, vascular and metabolic measures)

	Body Composition*		Inflammatory Markers**	
	Adjusted OR (CI)*	p Value	Adjusted OR (CI)*	p Value
Infant birth weight (kg)	0.83 (.56, 1.22)	0.339	.87 (.59, 1.30)	0.503
Low birth weight (<2500 g)	1.37 (.68, 2.75)	0.376	1.17 (.58, 2.36)	0.655
Preterm (<37 weeks)	1.96 (.79, 4.82)	0.146	2.01 (.81, 4.98)	0.132
Low birth weight and Preterm	2.64 (.86, 8.12)	0.091	2.49 (.82, 7.59)	0.108
	Vascular measures†		Metabolic measures ‡	
	Adjusted OR (CI)*	p Value	Adjusted OR (CI)*	p Value
Infant birth weight (kg)	.78 (.52, 1.17)	0.230	0.85 (.57, 1.25)	0.402
Low birth weight (<2500 g)	1.44 (.71, 2.93)	0.313	1.29 (.65, 2.60)	0.468
Preterm (<37 weeks)	2.77 (1.06, 7.24)	0.037	1.84 (.73, 4.66)	0.199
Low birth weight and Preterm	4.21 (1.23-14.45)	0.022	2.21 (.70, 6.96)	0.199

All models adjusted for age, race, HDL cholesterol, smoking, low SES, maternal age <20, statin use
* BMI, visceral fat (log), abdominal circumference added to model
** Il-6 (log), CRP (log) added to model
† Systolic blood pressure, diastolic blood pressure, PWV (log) and hypertension added to model
‡ Glucose (log), diabetes, triglycerides (log) added to model

4.6. LITERATURE CITED

1. Smith, G., J. Pell, and D. Walsh, *Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births.* Lancet, 2001. **357**(9273): p. 2002-6.
2. Davey Smith, G., S. Harding, and M. Rosato, *Relation between infants' birth weight and mothers' mortality: prospective observational study.* BMJ, 2000. **320**(7238): p. 839-40.
3. Irgens, H., et al., *Long term mortality of mothers and fathers after pre-eclampsia: population based cohort.* BMJ, 2001. **323**(7323): p. 1213-17.
4. Davey Smith, G., et al., *Birth dimensions of offspring, premature birth, and the mortality of mothers.* Lancet, 2000. **356**: p. 2066-67.
5. Walker, B., et al., *Contribution of parental blood pressures to association between low birth weight and adult high blood pressure: cross sectional study.* BMJ, 1998. **316**: p. 834-7.
6. Lawlor, D., G. Davey Smith, and S. Ebrahim, *Birth weight of offspring and insulin resistance in late adulthood: cross sectional survey.* BMJ, 2002. **325**: p. 359-62.
7. Davey Smith, G., et al., *Birth weight of offspring and mortality in the Renfrew and Paisley study: prospective observational study.* BMJ, 1997. **315**(717): p. 1189-1193.
8. Sattar, I. and I. Greer, *Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening?* BMJ, 2002. **325**: p. 157-160.
9. Churchill, D., I. Perry, and M. Beevers, *Ambulatory blood pressure in pregnancy and fetal growth.* Lancet, 1997. **349**: p. 7-10.
10. Sheppard, B. and J. Bonnar, *The ultrastructure of the arterial supply of the human placenta in pregnancy complicated by fetal growth restriction.* Br J Obstet Gynaecol, 1976. **83**: p. 948-59.
11. Germain, A., et al., *Preterm labor: placental pathology and clinical correlation.* Obstetrics and Gynecology, 1999. **94**(284-289).
12. Goldenberg, R., J. Iams, and B. Mercer, *The preterm prediction study: the value of new vs. standard risk factors.* American Journal of Public Health, 1998. **88**(2): p. 233-8.
13. Silver, R., B. Schwinzer, and J. McGregor, *Interleukin-6 levels in amniotic fluid in normal and abnormal pregnancies: preeclampsia, small for gestational age fetuses, and preterm labor.* Am J Obstet Gynecol, 1993. **169**(5): p. 1101-5.
14. Bartha, J., R. Romero-Carmona, and R. Comino-Delgado, *Inflammatory cytokines in intrauterine growth retardation.* Acta Obstet Gynecol Scand, 2003. **82**: p. 1099-102.
15. Ridker, P., et al., *C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women.* NEJM, 2000. **342**(12): p. 836-43.
16. Visser, M., et al., *Leg muscle mass and composition in relation to lower extremity performance in men and women aged 70 to 79: the Health, Aging and Body Composition Study.* JAGS, 2002. **50**(5): p. 897-904.
17. Rooks, R., et al., *The association of race and socioeconomic status with cardiovascular disease indicators among older adults in the Health, Aging, and Body Composition Study.* Journal of Gerontology: Social Sciences, 2002. **57B**(4): p. S247-S256.
18. Roberts, J. and K. Lain, *Recent insights into the pathogenesis of pre-eclampsia.* Placenta, 2002. **23**: p. 359-372.

19. Chesley, L., J. Annitto, and R. Cosgrove, *The remote prognosis of eclamptic women: sixth periodic report.* Am J Obstet Gynecol, 1976. **124**: p. 446-59.
20. Sibai, B., A. El-Nazer, and A. Gonzalez-Ruiz, *Severe preeclampsia in young primigravid women: subsequent pregnancy outcome and remote prognosis.* Am J Obstet Gynecol, 1986. **155**: p. 1011-6.
21. Ananth, C., A. Peedicayil, and D. Savitz, *Effect of hyptertensive diseases in pregnancy on birthweight, gestational duration, and small-for-gestational age births.* Epidemiology, 1995. **6**: p. 391-395.
22. Haelterman, E., et al., *Effect of uncomplicated chronic hypertension on the risk of small-for-gestational age birth.* American Journal of Epidemiology, 1997. **145**(8): p. 689-695.
23. Waugh, J., et al., *Birth weight and 24-hour ambulatory blood pressure in nonproteinuric hypertensive pregnancy.* Am J Obstet Gynecol, 2000. **183**(3): p. 633-637.
24. Seidman, D., et al., *Accuracy of mothers' recall of birthweight and gestational age.* British Journal of Obstetrics and Gynaecology, 1987. **94**(8): p. 731-5.
25. Fried, L., et al., *The Cardiovascular Health Study: design and rationale.* Annals of Epidmiology, 1991. **1**(3): p. 263-276.
26. Ives, D., A. Fitzpatrick, and D. Bild, *Surveillance and ascertainment of cardiovascular events: the Cardiovascular Health Study.* Annals of Epidmiology, 1995. **5**: p. 278-285.
27. Kuller, L., et al., *Subclinical disease as an independent risk factor for cardiovascular disease.* Circulation, 1995. **92**(4): p. 720-726.
28. Newman, A., et al., *Coronary artery calcification in older adults with minimal clinical or subclinical cardiovascular disease.* Journal of the American Geriatrics Society, 2000. **48**(3): p. 256-263.
29. Cesari, M., et al., *Inflammatory markers and cardiovascular disease (The Health, Aging and Body Composition[HealthABC] Study).* American Journal of Cardiology, 2003. **92**: p. 522-528.
30. National Cholesterol Education Program, *Third Report of the National Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)*, L.a.B.I. National Heart, NIH, Editor. 2002.
31. Matthews, D., et al., *Homeostasis model assessment: insuline resistance and beta-cell function from fasting glucose and insulin concentrations in man.* Diabetologia, 1985. **28**: p. 412-19.
32. Tranquilli, A., et al., *Normotensive women with intrauterine growth retardation show increased diastolic pressure in automated blood pressure monitoring.* Am J Obstet Gynecol, 1993. **168**(319): p. A76.
33. David, R. and J. Collins, *Differing birth weight among infants of U.S.-born Blacks, African-born Blacks and U.S.-born Whites.* NEJM, 1997. **337**(17): p. 1209-1214.
34. Collins, J. and R. David, *The differential effect of traditional risk factors on infant birthweight among Blacks and Whites in Chicago.* Am J Public Health, 1990. **80**: p. 679-81.
35. Shiono, P. and M. Klebanoff, *Ethnic differences in preterm and very preterm delivery.* Am J Public Health, 1986. **76**(11): p. 1317-21.
36. Abrams, B., et al., *Maternal weight gain and preterm delivery.* Obstetrics and Gynecology, 1989. **74**: p. 577-83.

37. Mosca, L., et al., *Cardiovascular disease in women: a statement for healthcare professionals from the American Heart Association.* Circulation, 1997. **96**(7): p. 2468-82.
38. Tomeo, C., et al., *Reproducibility and validity of maternal recall of pregnancy-related events.* Epidemiology, 1999. **10**(6): p. 774-7.
39. Olson, J., et al., *Medical record validation of maternally reported birth characteristics and pregnancy-related events: a report from the Children's Cancer Group.* Am J Epidemiol, 1997. **145**(1): p. 58-67.

5. DISCUSSION

This cross sectional study of the association between infant characteristics and maternal cardiovascular risk involved the retrospective collection of pregnancy history data from a cohort of well-functioning older women. In a small sub-study we were able to confirm the accuracy and reliability of maternal recall of infant birth weight collected on average of 57 after delivery, and we demonstrated that birth weight was recalled with particular precision for first births. We therefore were able to combine information about pregnancy history with a well-characterized, robust set of cardiovascular endpoints, body composition variables, and sociodemographic characteristics to describe the association between delivery of a low birth weight or preterm infant and a woman's remote cardiovascular disease risk.

Our findings suggest that women who had delivered a low birth weight infant vs. a normal weight infant (after excluding pregnancies complicated by preeclampsia or hypertension) had elevations in inflammatory, metabolic and vascular measures independent of age, race, BMI, and lifetime exposure to cigarette smoking. In addition, older women who delivered a first birth that was preterm had an increased risk for clinical cardiovascular disease after adjusting for sociodemographic characteristics, smoking exposure, and comorbidities. Women who had delivered small and early infants appeared to have an even higher risk for clinical cardiovascular disease. This was particularly true for women with hypertension, suggesting that maternal vascular disease may be a moderating factor. Our results should be viewed as preliminary, as many of estimates were imprecise. However, our findings raise the possibility that occult maternal vascular disease may contribute to LBW and preterm delivery, and could identify women who may benefit from screening and intervention for cardiovascular disease.

To our knowledge, this study is the first to investigate the association between LBW or preterm delivery and maternal cardiovascular morbidity in a population of older women, adjusted for a variety of physical, biologic and sociodemographic correlates. We were able to investigate possible pathways implicated in this association, and our findings suggest the importance of continued work in this area.

5.1. FUTURE RESEARCH

Our collection of pregnancy data via maternal recall limited our ability to characterize LBW and preterm delivery. It is likely that the components of LBW, idiopathic preterm delivery and growth restriction, may involve distinct or even overlapping pathways leading to the pregnancy characteristics we were able to measure. Our findings suggest that perhaps the convergence of more than one of these pathways could lead to the worst infant prognosis (i.e., the smallest babies), and the highest maternal cardiovascular risk. These questions merit additional investigation.

Future studies in this area will require more comprehensive data regarding pregnancy characteristics. Gestational age and additional markers of infant growth such as head circumference will be important to distinguish between infants that were growth restricted but not preterm, infants that were growth restricted and preterm, and infants that were preterm but grew appropriately. There is evidence, for example, that placental insufficiency leads to fetal growth restriction [1] as well as preterm delivery. [2] However, efforts to distinguish biologic pathways, perhaps via placental pathology [3], that lead to IUGR and/or preterm delivery will be

important to further understand and investigate the relationships between these pregnancy outcomes and remote maternal prognosis.

5.1.1. Maternal vascular disease, pregnancy outcomes and cardiovascular disease risk

Our most significant findings were those suggesting that LBW or preterm delivery may be associated with cardiovascular risk in women through maternal vascular disease that may remain occult during pregnancy. We found elevations in systolic blood pressure and pulse pressure in women who had delivered a LBW vs. normal weight infant many years in the past. In addition, we found that women with hypertension who delivered a preterm infant had a particularly elevated risk for clinical cardiovascular disease. Our findings need to be replicated and expanded in populations where gestational age, infant birth weight, maternal body composition, and pregnancy complications such as preeclampsia and hypertension can be better characterized.

Prospective studies of women with growth restricted or preterm pregnancies compared to women with normal pregnancies are needed, and analysis should be expanded to examine women with multiple pregnancies complicated by LBW or preterm delivery as women with recurrent events may have a particularly elevated cardiovascular risk. Measurement of the same markers that we investigated (blood pressures, pulse pressures, insulin, glucose, IL-6, CRP) will be important, as well as additional markers of endothelial function. Future studies that examine maternal endpoints more proximal to the growth restricted or preterm delivery will be necessary. Ideally, measurements would be done during pregnancy as well as five, ten, twenty, and forty years post partum in order to address the temporal questions that were raised by our study. Many

existing cohorts are available to investigate these questions, and these could be important next steps for additional analysis. In particular, it will be important to determine if women who deliver growth restricted or preterm pregnancies enter and leave these pregnancies with detectable differences in vascular, metabolic or inflammatory markers. This will help us determine when in the life course the differences that we detected emerge.

5.1.2. Infant characteristics and maternal body composition

One particularly interesting finding of this research that has not previously been described is the distinct body composition of women, at age 80, who delivered a LBW first infant. While it is well documented that small women deliver small babies [4], it has also been found that maternal waist circumference is positively associated with infant birth weight. [5] These observations suggest that women who delivered small or preterm infants accumulated central adioposity after the index pregnancy, but this question warrants additional prospective investigation. In addition, it will be important to investigate differential effects of body composition between white and black women. Other Health ABC investigators have suggested that regional fat depots in blacks may have different physiologic function than those in whites that could contribute to higher rates of hypertension among blacks [6], and potentially to higher rates of poor pregnancy outcomes. Additional investigation of the relationship between body composition and poor pregnancy outcomes will require study of racially diverse populations in order to better understand any race-specific differences.

5.1.3. Infant birth weight, preterm delivery and insulin resistance

Consistent with the work of Lawlor, et al, [7] we found that infant birth weight was inversely related to maternal insulin resistance in older women. There was no association, however, between infant birth weight and diabetes (p=0.848) or metabolic syndrome (p=0.667) suggesting a more recent pathology which had not progressed. Mothers with gestational glucose intolerance tend to have heavier babies [8], and are more likely to be insulin resistant and to develop diabetes later in life [9]. Additional work is needed to determine any association between IUGR or preterm delivery and maternal insulin resistance during and after pregnancy. This prospective work would help identify the temporal nature and etiology of the insulin resistance detected in our study and the Lawlor study. In addition, further work in this area should also include adequate numbers of black and white women, as our results suggested that insulin levels were elevated among white women many years after delivery of a LBW infant, but not among black women with LBW infants.

5.1.4. Inflammation, LBW, preterm delivery and maternal cardiovascular risk

There has been strong evidence of an association between chronic inflammation and preterm delivery, particularly preterm births occurring prior to 33 weeks gestation [10]. In addition, upregulation of inflammatory cytokines has been implicated in cardiovascular risk in women [11]. While the older women in our study with a LBW infant had elevations in IL-6 and CRP, these inflammatory markers did not appear to be associated with increased risk for clinical cardiovascular disease risk at age 80. These findings appear to contradict those of Tracey [12] who found that CRP was associated with incident cardiovascular events among older women in

the Cardiovascular Health Study, and those of Cesari [13] who found that elevations in IL-6 and CRP were associated with both subclinical and clinical cardiovascular disease in men and women combined from the Health ABC study. We did not find elevations in IL-6 or CRP among women with subclinical or clinical cardiovascular disease, although median levels for black and white women in our study population were similar to those reported in women from both the Pittsburgh and Memphis field centers by Visser. [14] Additional work is needed to better understand the association between delivery of a LBW or preterm infant, maternal levels of inflammation both during and after pregnancy which itself is an inflammatory state, and how these levels change over the course of a woman's lifetime after adjustment for weight gain, visceral fat, insulin resistance and cigarette smoking.

5.1.5. LBW, preterm delivery, cigarette smoking and maternal prognosis

Cigarette smoking was an important covariate in our work as it was associated with infant birth weight and cardiovascular disease. As expected, women who delivered LBW infants had higher rates of smoking and higher levels of smoking as measured in pack years compared to women with normal weight infants. [15-17] We also found the well documented association between smoking and clinical cardiovascular disease. [18, 19] Our small population of women who reported infants born both small and preterm had the highest rates of smoking and appeared to have the highest risks for clinical cardiovascular disease. Lain, et al, has suggested that smoking may interact differently with normal and abnormal pregnancies, and that smoking may be associated with both abnormal placentation and maternal endothelial function. [20] It is possible that the additional insult of nicotine during pregnancy on a maternal vascular system

predisposed to reduced placental perfusion (but without the entire maternal syndrome that contributes to preeclampsia) may escalate the risk for growth restriction or preterm delivery. There is evidence that pregnancy risks associated with smoking interact with maternal age [17], providing some support for this notion of additive risk. The possibility of a differential effect of smoking on pregnancies complicated by preterm delivery or IUGR requires further investigation, ideally in a large prospective study of mothers with well characterized pregnancy, cotinine, and vascular measures and long term follow up.

5.2. LITERATURE CITED

1. Sheppard, B. and J. Bonnar, *The ultrastructure of the arterial supply of the human placenta in pregnancy complicated by fetal growth restriction.* Br J Obstet Gynaecol, 1976. **83**: p. 948-59.
2. Germain, A., et al., *Preterm labor: placental pathology and clinical correlation.* Obstetrics and Gynecology, 1999. **94**(284-289).
3. Holzman, C., et al., *Pregnancy outcomes and community health: The POUCH study of preterm delivery.* Paediatric Perinatal Epidemiology, 2001. **15 (Suppl 2)**: p. 136-158.
4. Green, J., et al., *Influence of maternal body habitus and glucose tolerance on birth weight.* Obstetrics and Gynecology, 1991. **78**(2): p. 235-239.
5. Brown, J., et al., *Maternal waist-to-hip ratio as a predictor of newborn size; results of the Diana Project.* Epidemiology, 1995. **7**(1): p. 62-66.
6. Ding, J., et al., *The association of regioanl fat depots with hypertension in older persons of white and african american ethnicity.* American Journal of Hypertension, 2004. **17**: p. 971-976.
7. Lawlor, D., G. Davey Smith, and S. Ebrahim, *Birth weight of offspring and insulin resistance in late adulthood: cross sectional survey.* BMJ, 2002. **325**: p. 359-62.
8. Scholl, T., et al., *Maternal glucose concentration influences fetal growth, gestation and pregnancy complications.* Am J Epidemiol, 2001. **154**: p. 514-20.
9. Dornhorst, A. and M. Rossi, *Risk and prevention of type 2 diabetes in women with gestational diabetes.* Diabetes Care, 1998. **21(suppl 2)**: p. 43-9S.
10. Goldenberg, R., J. Hauth, and W. Andrews, *Mechanisms of disease: intrauterine infection and preterm delivery.* NEJM, 2000. **342**(20): p. 1500-7.
11. Ridker, P., et al., *C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women.* NEJM, 2000. **342**(12): p. 836-43.
12. Tracy, R., et al., *Relationship of C-Reactive Protein to Risk of Cardiovascular Disease in the Elderly.* Arteriosclerosis, Thrombosis, and Vascular Biology, 1997. **17**(6): p. 1121-1127.
13. Cesari, M., et al., *Inflammatory markers and cardiovascular disease (The Health, Aging and Body Composition[HealthABC] Study).* American Journal of Cardiology, 2003. **92**: p. 522-528.
14. Visser, M., et al., *Realtionship of interleukin-6 and tumor necrosis factor-alpha with muscle mass and muscle stregnth in elderly men and women: The Health ABC Study.* Journal of Gerontology: Medical Sciences, 2002. **57**(5): p. M326-M332.
15. Abrams, B. and V. Newman, *Small-for-gestational age birth: maternal predictors and comparison with risk factors of spontaneous delivery in the same cohort.* Am J Obstet Gynecol, 1991. **164**: p. 785-90.
16. Shiono, P. and M. Klebanoff, *Ethnic differences in preterm and very preterm delivery.* Am J Public Health, 1986. **76**(11): p. 1317-21.
17. Fox, S., T. Koepsell, and J. Daling, *Birth weight and smoking during pregnancy-effect modification by maternal age.* Am J Epidemiol, 1994. **139**: p. 1008-15.

18. Khot, U., et al., *Prevalence of conventional risk factors in patients with coronary heart disease.* JAMA, 2003. **290**(7): p. 898-904.
19. Njolstad, I., E. Arnesen, and P. Lund larsen, *Body height, cardiovascular risk factors, and risk of stroke in middle-aged men and women: a 14-year follow up study of the Finnmark Study.* Circulation, 1996. **94**: p. 2877-2882.
20. Lain, K., et al., *Smoking during pregnancy is associated with alterations in markers of endothelial function.* Am J Obstet Gynecol, 2003. **189**(4): p. 1196-1201.

6. APPLICATION TO PUBLIC HEALTH

Describing an association between pregnancy outcomes and maternal chronic disease risk contributes new insight into the persistent public health challenges of low birth weight and preterm delivery. This work builds on the emerging evidence that occult maternal vascular disease may lead to placental insufficiency, resulting in infants born too small or too early. Our work contributes new information by examining intermediate cardiovascular measures and pathways that may moderate this relationship. Interventions to reduce cardiovascular risk, such as smoking cessation and increased physical activity, may also alter risks for poor pregnancy outcomes.

In addition, if an undetected predisposition for chronic disease is associated with LBW or preterm delivery, these outcomes could help identify a subset of women who could benefit from screening and intervention to reduce cardiovascular risk. Identification of high risk women prior to the menopause, when clinical attention to these risks typically begins, would help initiate treatment perhaps in time to delay onset of disease. Pregnancy care is often the only clinical care a woman receives during her reproductive years. Poor pregnancy outcomes could mark women who should be screened for cardiovascular risk at a relatively young age and referred for on-going routine clinical intervention following the post partum visit.

This work also contributes potentially important information to reduce racial disparities in pregnancy and cardiovascular outcomes. The rates of low birth weight, preterm delivery and cardiovascular disease among black women are about twice that of white women. Our findings suggest that there may be some race-specific risks that moderate the association between pregnancy outcomes and cardiovascular disease, and these warrant additional investigation.

Our study suggests that infant outcomes might be affected by a mother's overall health status as she enters pregnancy. If these results are confirmed by other investigators and in other populations, public health efforts to improve the cardiovascular health status of young women of reproductive age may help reduce the burden of poor pregnancy outcomes as well as improve the health of women as they age.

BIBLIOGRAPHY

Abrams, B. and V. Newman (1991). "Small-for-gestational age birth: maternal predictors and comparison with risk factors of spontaneous delivery in the same cohort." Am J Obstet Gynecol **164**: 785-90.

Abrams, B., V. Newman, et al. (1989). "Maternal weight gain and preterm delivery." Obstetrics and Gynecology **74**: 577-83.

Ananth, C., A. Peedicayil, et al. (1995). "Effect of hyptertensive diseases in pregnancy on birthweight, gestational duration, and small-for-gestational age births." Epidemiology **6**: 391-395.

Barker, D. and C. Osmond (1986). "Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales." Lancet **8489**(1): 1077-81.

Bartha, J., R. Romero-Carmona, et al. (2003). "Inflammatory cytokines in intrauterine growth retardation." Acta Obstet Gynecol Scand **82**: 1099-102.

Beard, C., V. Fuster, et al. (1984). "Reproductive history in women with coronary heart disease: a case-control study." Am J Epidemiol **120**(1): 108-114.

Benowitz, N. (1991). "Nicotine replacement therapy during pregnancy." JAMA **266**: 3174-3177.

Brown, J., J. Potter, et al. (1995). "Maternal waist-to-hip ratio as a predictor of newborn size; results of the Diana Project." Epidemiology **7**(1): 62-66.

Carey, J., M. Klebanoff, et al. (2000). "Metronidazole to prevent preterm delivery in pregnant women with asymptomatic bacterial vaginosis." NEJM **342**(8): 534-40.

Cesari, M., B. Penninx, et al. (2003). "Inflammatory markers and cardiovascular disease (The Health, Aging and Body Composition[HealthABC] Study)." American Journal of Cardiology **92**: 522-528.

Chambers, J., L. Fusi, et al. (2001). "Association of maternal endothelial dysfunction with preeclampsia." JAMA **285**(12): 1607-12.

Chesley, L., J. Annitto, et al. (1976). "The remote prognosis of eclamptic women: sixth periodic report." Am J Obstet Gynecol **124**: 446-59.

Churchill, D., I. Perry, et al. (1997). "Ambulatory blood pressure in pregnancy and fetal growth." Lancet **349**: 7-10.

Collins, J. and R. David (1990). "The differential effect of traditional risk factors on infant birthweight among Blacks and Whites in Chicago." Am J Public Health **80**: 679-81.

Davey Smith, G., S. Harding, et al. (2000). "Relation between infants' birth weight and mothers' mortality: prospective observational study." BMJ **320**(7238): 839-40.

Davey Smith, G., C. Hart, et al. (1997). "Birth weight of offspring and mortality in the Renfrew and Paisley study: prospective observational study." BMJ **315**(717): 1189-1193.

Davey Smith, G., E. Whit ley, et al. (2000). "Birth dimensions of offspring, premature birth, and the mortality of mothers." Lancet **356**: 2066-67.

David, R. and J. Collins (1997). "Differing birth weight among infants of U.S.-born Blacks, African-born Blacks and U.S.-born Whites." NEJM **337**(17): 1209-1214.

Dekker, G. and B. Sibai (2001). "Primary, secondary and tertiary prevention of preeclampsia." Lancet **357**: 209-215.

denTonkelaar, I., J. Seidell, et al. (1990). "Fat distribution in relation to age, degree of obesity, smoking habits, parity, and estrogen use: a cross-sectional study in 11,825 Dutch women participating in the DOM-project." Int J Obesity **14**(9): 753-61.

Despres, J.-P. (1993). "Abdominal obesity as important component of insulin resistance syndrome." Nutrition **9**(452-459).

Ding, J., M. Visser, et al. (2004). "The association of regioanl fat depots with hypertension in older persons of white and african american ethnicity." American Journal of Hypertension **17**: 971-976.

Dornhorst, A. and M. Rossi (1998). "Risk and prevention of type 2 diabetes in women with gestational diabetes." Diabetes Care **21(suppl 2)**: 43-9S.

Dvorak, D., W. DeNino, et al. (1999). "Phenotypic characteristics associated with insulin resistance in metabolically obese but normal-weight young women." Diabetes **48**: 2210-2214.

Eriksson, J., T. Forsen, et al. (2002). "Effects of size at birth and childhood growth on insulin resistance syndrome in elderly individuals." Diabetologia **45**(3): 342-8.

Eskenazi, B., L. Fenster, et al. (1991). "A multivariate analysis of risk factors for preeclampsia." JAMA **266**: 237-241.

Eskenazi, B., L. Fenster, et al. (1993). "Fetal growth retardation in infants of multiparous and nulliparous women with preeclampsia." Am J Obstet Gynecol **169**: 1112-1118.

Fang, J., S. Madhavan, et al. (1999). "The influence of maternal hypertension on low birth weight: differences among ethnic populations." Ethnicity and Disease **9**(369-76).

Feinstein, A. and D. Cichetti (1990). "High agreement but low kappa: the problem of two paradoxes." Journal of Clinical Epidemiology **1990**(43): 6.

Flegal, K., R. Ness, et al. (1990). "Parity and high density lipoprotein (HDL) cholesterol levels in white women from the Second National Health and Nutrition Examination Survey (NHANES II). (Abstract)." American Journal of Epidemiology **132**: 766.

Forsen, T., J. Eriksson, et al. (1999). "Growth in utero and during childhood among women who develop coronary heart disease: longitudinal study." BMJ **319**: 1403-7.

Forster, J., E. Bloom, et al. (1986). "Reproductive history and body mass index in black and white women." Prev Med **15**(6): 685-91.

Fox, S., T. Koepsell, et al. (1994). "Birth weight and smoking during pregnancy-effect modification by maternal age." Am J Epidemiol **139**: 1008-15.

Fried, L., N. Borhani, et al. (1991). "The Cardiovascular Health Study: design and rationale." Annals of Epidmiology **1**(3): 263-276.

Frisbie, W., M. WBiegler, et al. (1997). "Racial and ethnic differences in determinants of intrauterine growth retardation and other compromised birth outcomes." Am J Public Health **87**: 1977-83.

Germain, A., J. Carvajal, et al. (1999). "Preterm labor: placental pathology and clinical correlation." Obstetrics and Gynecology **94**(284-289).

Goldenberg, R. and S. Cliver (1997). "Small for gestation age and intrauterine growth restriction: definitions and standards." Clin Obstet Gynecol **40**: 704-14.

Goldenberg, R., R. Davis, et al. (1993). "Maternal risk factors and their influence on fetal anthropotetric measurements." Am J Obstet Gynecol **168**: 1197-1205.

Goldenberg, R., J. Hauth, et al. (2000). "Mechanisms of disease: intrauterine infection and preterm delivery." NEJM **342**(20): 1500-7.

Goldenberg, R., J. Iams, et al. (1998). "The preterm prediction study: the value of new vs. standard risk factors." American Journal of Public Health **88**(2): 233-8.

Goodpaster, B., S. Krishnaswami, et al. (2003). "Association between regional adipose tissue distribution and both type 2 diabetes and impaired glucose tolerance in elderly men and women." Diabetes Care **26**(2): 372-379.

Gordon, T., W. Castelli, et al. (1977). "Diabetes, blood lipids, and the role of obestiy in coronary heart diease risk for women. The Framingham Study." Annals of Internal Medicine **87**(4): 393-7.

Green, J., L. Schumacher, et al. (1991). "Influence of maternal body habitus and glucose tolerance on birth weight." Obstetrics and Gynecology **78**(2): 235-239.

Greenberg, D., B. Yoder, et al. (1993). "Effect of maternal race on outcome of preterm infants in teh military." Pediatrics **91**: 572-7.

Haelterman, E., G. Breart, et al. (1997). "Effect of uncomplicated chronic hypertension on the risk of small-for-gestational age birth." American Journal of Epidemiology **145**(8): 689-695.

Haggard, E., A. Brekstad, et al. (1960). "On the reliability of the anamnestic interview." Journal of Abnormal Social Psychology **61**: 49-64.

Hattersley, A. and J. Tooke (1999). "The fetal insulin hypothesis: an alternative explanation of the association of low birth weight with diabetes and vascular disease." Lancet **353**: 1789-92.

Henriksen, R. and T. Clausen (2002). "The fetal origins hypothesis: placential insufficiency and inheritancce versus maternal malnutrition in well-nourished populations." Acta Obstet Gynecol Scand **81**: 112-14.

Hillier, L., R. Nugent, et al. (1995). "Association between bacterial vaginosis and preterm delivery of a low-birth-weight infant." NEJM **333**: 1737-1742.

Holzman, C., B. Bullen, et al. (2001). "Pregnancy outcomes and community health: The POUCH study of preterm delivery." Paediatric Perinatal Epidemiology **15 (Suppl 2)**: 136-158.

Hubel, C., S. Snaedal, et al. (2000). "Dyslipoproteinaemia in postmenopausal women with a history of preeclampsia." Fr J Obstet Gynaecol **107**(776-84).

Iams, J. and R. Creasy (2004). Preterm labor and delivery. Maternal and Fetal Medicine: Principles and Practice. R. Creasy and R. Resnic. Philadelphia, Saunders**:** 623-61.

Iams, J., R. Goldenberg, et al. (1998). "The preterm prediction study: recurrent risk of spontaneous preterm birth." Am J Obstet Gynecol **178**: 1035-40.

Institute of Medicine (1985). Preventing low birth weight. Washington, DC, National Academy Press.

Irgens, H., L. Reisaeter, et al. (2001). "Long term mortality of mothers and fathers after pre-eclampsia: population based cohort." BMJ **323**(7323): 1213-17.

Ives, D., A. Fitzpatrick, et al. (1995). "Surveillance and ascertainment of cardiovascular events: the Cardiovascular Health Study." Annals of Epidmiology **5**: 278-285.

Kannel, W. and P. Wilson (1995). "Risk factors that attenuate the female cornary disease advantage." Archives of Internal Medicine **155**: 57-61.

Kaye, S., A. Folsom, et al. (1990). "The association of body fat distribution with lifestyle and reproductive factors in a population study of postmenopausal women." Int J Obesity **14**(7): 583-91.

Khong, T., F. DeWolf, et al. (1986). "Inadequate maternal vascular response to placentation in pregnancies complicated by small-for-gestational age infants." Br J Obstet Gynaecol **93**: 1049-59.

Khot, U., M. Khot, et al. (2003). "Prevalence of conventional risk factors in patients with coronary heart disease." JAMA **290**(7): 898-904.

Kim, Y., E. RBujold, et al. (2003). "Failure of physiologic transformation of the spiral arteries in patients with preterm labor and intact membranes." Am J Obstet Gynecol **189**(4): 1063-1069.

Klebanoff, M., B. Graubard, et al. (1984). "Low birth weight across the generations." JAMA **252**(17): 2423-7.

Kohrt, W., J. Kirwan, et al. (1993). "Insulin resistance in aging is related to abdominal obesity." Diabetes **42**: 273-281.

Korn, A., G. Bolan, et al. (1995). "Plasma cell endometritis in women with symptomatic bacterail vaginosis." Obstetrics and Gynecology **85**(387-90).

Kritz-Silverstein, D., E. Barrett-Connor, et al. (1992). "The relationship between multiparity and lipoprotein levels in older women." J Clin Epidemiology **45**(7): 761-67.

Kuller, L., L. Shemanski, et al. (1995). "Subclinical disease as an independent risk factor for cardiovascular disease." Circulation **92**(4): 720-726.

Labarthe, D. (1998). Epidemiology and Prevention of Cardiovascular Disease: A Global Challenge, Aspen Publications.

Lain, K., J. Wilson, et al. (2003). "Smoking during pregnancy is associated with alterations in markers of endothelial function." Am J Obstet Gynecol **189**(4): 1196-1201.

Landis, J. and G. Koch (1977). "The measurement of observer agreement for categorical data." Biometrics **33**: 159-74.

LaVecchia, C., A. Decarli, et al. (1987). "Menstrual and reproductive factors and the risk of myocardioal infarction in women under fifty-five years of age." Am J Obstet Gynecol **157**(15): 1108-12.

Law, C. and A. Shiell (1996). "Is blood pressure inversely related to birth weight? The strength of the evidence from a systematic review of the literature." Journal of Hypertension **14**(935-41).

Lawlor, D., G. Davey Smith, et al. (2002). "Birth weight of offspring and insulin resistance in late adulthood: cross sectional survey." BMJ **325**: 359-62.

Lederman, S. and A. Paxton (1998). "Maternal reporting of prepregnancy weight and birth outcome: consistency and completeness compared with the clinical record." Maternal and Child Health Journal **2**(2): 123-126.

Lin, C.-C., M. Lindheimer, et al. (1982). "Fetal outcome in hypertensive disorders of pregnancy." Am J Obstet Gynecol **142**: 255-260.

Lumey, L., A. Stein, et al. (1994). "Maternal recall of birthweights of adult children: validation by hospital and well baby clinic records." Int J Epidemiology **23**(5): 1006-1011.

Manson, J. and A. Spelsberg (1996). Risk modification in the diabetic patient. Prevention of Mycardial Infarction. J. Manson, P. Ridker, J. Gaziano and C. Hennekens. New York, NY, Oxford University Press**:** 249-250.

Martikainen, A., K. Heinonen, et al. (1989). "The effect of hypertension in prgnancy on fetal and neonatal condition." Int J Gynecol Obstet **30**: 213-20.

Matthews, D., J. Hosker, et al. (1985). "Homeostasis model assessment: insuline resistance and beta-cell function from fasting glucose and insulin concentrations in man." Diabetologia **28**: 412-19.

Matthews, K., L. Kuller, et al. (2001). "Changes in cardiovascular risk factors during the perimenopause and postmenopause and carotid artery atherosclerosis in healthy women." Stroke **32**(5): 1104-11.

Mattison, D., K. Damus, et al. (2001). "Preterm delivery: a public health perspective." Paediatric Perinatal Epidemiology **15**(supplement): 7-16.

McCormick, M. (1985). "The contribution of low birth weight to infant mortality and childhood morbidity." NEJM **312**: 82-90.

McDonald, A., B. Armstrong, et al. (1992). "Cigarette, alcohol, and coffee consumption and prematurity." Am J Public Health **82**: 82-90.

Medicine, I. o. (1985). Preventing low birth weight. Washington, DC, National Academy Press.

Monga, M. (2004). Maternal cardiovascular and renal adaptation to pregnancy. Maternal and Fetal Medicine: Principles and Practice. R. Creasy and R. Resnik. Philadelphia, Saunders**:** 111-20.

Mosca, L., J. Manson, et al. (1997). "Cardiovascular disease in women: a statement for healthcare professionals from the American Heart Association." Circulation **96**(7): 2468-82.

Muller, R. and P. Buttner (1994). "A critical discussion of intraclass correlation coefficients." Statistics in Medicine **13**: 2465-76.

National Center for Health Statistics (2002). Births: Final data for 2002**:** 114.

National Center for Health Statistics (2004). Health, United States.

National Cholesterol Education Program (2002). Third Report of the National Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). L. a. B. I. National Heart, NIH.

Ness, R., T. Harris, et al. (1993). "Number of pregnancies and the subsequent risk of cardiovascular disease." NEJM **328**(21): 1528-1533.

Ness, R., N. Markovic, et al. (2003). "Family history of hypertension, heart disease, and stroke among women awho develop hypertension in pregnancy." Obstetrics and Gynecology **102**(6): 1366-71.

Ness, R. and J. Roberts (1996). "Heterogeneous causes constituting the single syndrome of preeclampsia: a hypothesis and its implications." Am J Obstet Gynecol **105**: 1365-70.

Ness, R., H. Schotland, et al. (1994). "Reproductive history and coronary heart disease risk in women." Epidemiology Reviews **16**(2): 298-314.

Newman, A., B. Naydeck, et al. (2000). "Coronary artery calcification in older adults with minimal clinical or subclinical cardiovascular disease." Journal of the American Geriatrics Society **48**(3): 256-263.

Niewenweg, R., M. Smit, et al. (2003). "Adult height corrected for shrinking and secular trend." Annals of Human Biology **30**(5): 563-569.

Njolstad, I., E. Arnesen, et al. (1996). "Body height, cardiovascular risk factors, and risk of stroke in middle-aged men and women: a 14-year follow up study of the Finnmark Study." Circulation **94**: 2877-2882.

Nuwayhid, B., T. Nguyen, et al. (1998). Maternal physiology. Essentials of Obstetrics and Gynecology. N. Hacker and J. Moore. Philadelphia, Saunders Company**:** 85-99.

Olson, J., X. Shu, et al. (1997). "Medical record validation of maternally reported birth characteristics and pregnancy-related events: a report from the Children's Cancer Group." Am J Epidemiol **145**(1): 58-67.

Palmer, J., L. Rosenberg, et al. (1992). "Reproductive factors and risk of myocardial infarction." Am J Epidemiol **136**(4): 408-416.

Pijnenborg, R. (1996). "The placental bed." Hypertens Pregnancy **15**: 7-23.

Resnik, R. and R. Creasy (2004). Intrauterine Growth Restriction. Maternal and Fetal Medicine: Principles and Practices. R. Creasy and R. Resnik. Philadelphia, Saunders**:** 495-512.

Ridker, P., C. Hennekens, et al. (2000). "C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women." NEJM **342**(12): 836-43.

Roberts, J. and D. Cooper (2001). "Pathogenesis and genetics of pre-eclampsia." Lancet **357**: 53-56.

Roberts, J. and K. Lain (2002). "Recent insights into the pathogenesis of pre-eclampsia." Placenta **23**: 359-372.

Rooks, R., E. Simonsic, et al. (2002). "The association of race and socioeconomic status with cardiovascular disease indicators among older adults in the Health, Aging, and Body Composition Study." Journal of Gerontology: Social Sciences **57B**(4): S247-S256.

Roquer, J., J. Figueras, et al. (1995). "Influence on fetal growth of exposure to tobacco smoke during pregnancy." Acta Paediatr **84**: 118-21.

Ross, R., L. Fortier, et al. (1996). "Separate associations between visceral and subcutaneous adipose tissue distribution, insulin and glucose levels in obese women." Diabetes Care **19**: 1404-11.

Ruderman, N., S. Schneider, et al. (1981). "The "metabolically-obese," normal-weight individual." Am J Clin Nutr **34**: 1617-21.

Sacks, G., K. Studena, et al. (1998). "Normal pregnancy and preeclampsia both produce inflammatory changes in peripheral blood leukocytes akin to those of sepsis." JAMA **179**(1): 80-6.

Salafia, C., V. Minior, et al. (1995). "Intrauterine growth restriction in infants of less than thirty-two weeks' gestation: associated placental pathologic features." Am J Obstet Gynecol **173**: 1049-57.

Sattar, I. and I. Greer (2002). "Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening?" BMJ **325**: 157-160.

Schieve, L., P. Geraldine, et al. (1999). "Validity of self-reported pregnancy delivery weight: an analysis of the 1988 National Maternal and Infnat Health Survey." Am J Epidemiol **150**(9): 947-956.

Scholl, T., S. M, et al. (2001). "Maternal glucose concentration influences fetal growth, gestation and pregnancy complications." Am J Epidemiol **154**: 514-20.

Schwertner, H., L. Torres, et al. (1987). "Cortisol and the hypercholesterolemia of pregnancy and labor." Atherosclerosis **67**: 237-244.

Scott, A., V. Moar, et al. (1981). "The relative contributions of different maternal factors in small-for-gestatinal age pregnancies." Eur J Obstet Gynecol Reprod Biol **12**: 157-65.

Seidman, D., P. Slater, et al. (1987). "Accuracy of mothers' recall of birthweight and gestational age." British Journal of Obstetrics and Gynaecology **94**(8): 731-5.

Sheppard, B. and J. Bonnar (1976). "The ultrastructure of the arterial supply of the human placenta in pregnancy complicated by fetal growth restriction." Br J Obstet Gynaecol **83**: 948-59.

Shiono, P. and M. Klebanoff (1986). "Ethnic differences in preterm and very preterm delivery." Am J Public Health **76**(11): 1317-21.

Shrout, P. and J. Fleiss (1979). "Intraclass correlations: uses in assessing rater reliability." Psychological Bulletin **86**(2): 420-8.

Sibai, B., A. El-Nazer, et al. (1986). "Severe preeclampsia in young primigravid women: subsequent pregnancy outcome and remote prognosis." Am J Obstet Gynecol **155**: 1011-6.

Silver, R., B. Schwinzer, et al. (1993). "Interleukin-6 levels in amniotic fluid in normal and abnormal pregnancies: preeclampsia, small for gestational age fetuses, and preterm labor." Am J Obstet Gynecol **169**(5): 1101-5.

Smith, G., J. Pell, et al. (2001). "Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births." Lancet **357**(9273): 2002-6.

Thomson, A., J. Telfer, et al. (1999). "Leukocytes infiltrate the myometrium during human parturition: further evidence that labour is an inflammatory process." Human Reproduction **14**(1): 229-36.

Tilley, B., A. Barnes, et al. (1985). "A comparison of pregnancy history recall and medical records." Am J Epidemiol **121**(2): 269-281.

Tomeo, C., J. Rich-Edwards, et al. (1999). "Reproducibility and validity of maternal recall of pregnancy-related events." Epidemiology **10**(6): 774-7.

Tracy, R. (2001). "Is visceral adiposity the "enemy within"?" Arteriosclerosis, Thrombosis, and Vascular Biology **21**: 881-883.

Tracy, R., R. Lemaitre, et al. (1997). "Relationship of C-Reactive Protein to Risk of Cardiovascular Disease in the Elderly." Arteriosclerosis, Thrombosis, and Vascular Biology **17**(6): 1121-1127.

Tranquilli, A., I. Harfouce, et al. (1993). "Normotensive women with intrauterine growth retardation show increased diastolic pressure in automated blood pressure monitoring." Am J Obstet Gynecol **168**(319): A76.

Visser, M., S. Kritchevsky, et al. (2002). "Leg muscle mass and composition in relation to lower extremity performance in men and women aged 70 to 79: the Health, Aging and Body Composition Study." JAGS **50**(5): 897-904.

Visser, M., M. Pahor, et al. (2002). "Realtionship of interleukin-6 and tumor necrosis factor-alpha with muscle mass and muscle stregnth in elderly men and women: The Health ABC Study." Journal of Gerontology: Medical Sciences **57**(5): M326-M332.

Walker, B., A. McConnachie, et al. (1998). "Contribution of parental blood pressures to association between low birth weight and adult high blood pressure: cross sectional study." BMJ **316**: 834-7.

Wang, X., B. Zuckerman, et al. (1995). "Familial aggregation of low birth weight among whites and blacks in the United States." NEJM **333**: 1744-1749.

Waugh, J., I. Perry, et al. (2000). "Birth weight and 24-hour ambulatory blood pressure in nonproteinuric hypertensive pregnancy." Am J Obstet Gynecol **183**(3): 633-637.

Writing group for the Women's Health Initiative Investigators (2002). "Risks and benefits of estrogen plus progestin in healthy postmenopausal women." JAMA **288**(3): 321-33.

Yawn, B., V. Suman, et al. (1998). "Maternal recall of distant pregnancy events." Journal of Clinical Epidemiology **51**(5): 399-405.

Yudkin, J., C. Stehouwer, et al. (1999). "C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue?" Arteriosclerosis, Thrombosis, and Vascular Biology **19**: 972-978.

Zeitlin, J., P. Ancel, et al. (2001). "Are risk factors the same for small for gestational age versus other preterm births." Am J Obstet Gynecol **185**(1): 208-15.