Life Course Influences on Insulin Resistance

Findings from the British Women's Heart and Health Study

DEBBIE A. LAWLOR, MPH
GEORGE DAVEY SMITH, MD
SHAH EBRAHIM, DM

OBJECTIVE — To assess the independent associations of a broad range of early life risk factors and adult obesity with adult insulin resistance.

RESEARCH DESIGN AND METHODS — This was a cross-sectional study of 1,394 women, aged 60–79 years, from 23 British towns.

RESULTS — There was a strong (independent of confounding factors, other early life factors, and adult waist-to-hip ratio) inverse association between birth weight and insulin resistance in women in the highest third of BMI (>28.77 kg/m^2): −0.12 (95% CI −0.19 to −0.04) log homeostasis model assessment (HOMA) score per 1 SD birth weight, but no association between birth weight and insulin resistance in women in the two lowest thirds of BMI (*P* for interaction = 0.04). Offspring birth weight, own leg length, and childhood manual social class did not interact with adult obesity and were all independently inversely associated with insulin resistance: −0.05 (−0.09 to −0.01) log HOMA score per 1 SD offspring birth weight, −0.09 (−0.12 to −0.06) log HOMA score per 1 SD leg length, and a −0.07 (−0.14 to 0.00) difference in log HOMA score between manual and nonmanual childhood social class. Childhood manual social class and shorter leg length were both independently associated with adverse lipid profiles. BMI and waist-to-hip ratio were independently positively associated with insulin resistance and with all other components of the insulin resistance syndrome.

CONCLUSIONS — Insulin resistance is an important risk factor for type 2 diabetes and coronary heart disease. Our results suggest that genetic factors, intrauterine environment, early childhood, and adult environmental factors are all relevant in determining adult insulin resistance.

Diabetes Care **26:97–103, 2003**

Several lines of research suggest that the pathogenesis of both type 2 diabetes and coronary heart disease begin in early life. Autopsy studies of U.S. combatants killed in the Korean and Vietnamese wars found that 77 and 45%, respectively, of the young men in these studies (mean age 22 years) had atherosclerosis (1,2). Low birth weight (3,4), childhood social class (5), and adult leg length (an indicator of childhood environmental exposures (6–8) have all been found to predict type 2 diabetes and coronary heart disease in later life. Insulin resistance appears to be an important mediating factor in all of these associations.

One explanation for the association between low birth weight and both type 2 diabetes and coronary heart disease is that poor intrauterine nutrition leads to not only small birth size but also, depending upon the timing of the nutritional deprivation, to "program" changes in glucose-insulin metabolism leading to insulin resistance and increased diabetes and coronary heart disease risk in later life (9). An alternative theory, the fetal insulin hypothesis, suggests that genetic polymorphisms that lead to both increased insulin resistance and insulin-mediated impaired fetal growth underlie the association between birth weight and diabetes and coronary heart disease (4,10). This latter hypothesis is supported by the finding that offspring birth weight is associated with increased risk of parental (in both mothers and fathers) insulin resistance, diabetes, and coronary heart disease, independently of socioeconomic position (11–14). Clearly an association between offspring birth weight and parental disease cannot be explained by intrauterine programming.

Leg length is a useful indicator of childhood nutrition. Interruption of growth at any stage in the life course leads to relatively short legs and long torso; this is particularly so in early childhood (15). In the 1946 British birth cohort, infant nutrition predicted adult leg length (6). The associations between both leg length and childhood manual social class and coronary heart disease also appear to be mediated through influences on insulin resistance (7,8,16).

These early life factors interact with each other and with adult obesity, which is a particularly strong determinant of insulin resistance (17). No previous study has assessed the independent associations of a broad range of early life risk factors and adult obesity with insulin resistance. The aim of the current study was to investigate the independent associations with insulin resistance of a broad range of early life factors: birth weight, offspring birth weight, leg length, and childhood social class together with adult general and central obesity.

RESEARCH DESIGN AND METHODS

Participants

The British Women's Heart and Health Study is a sample of women aged 60–79 years randomly selected from general

From the Department of Social Medicine, University of Bristol, Bristol, U.K.

Address correspondence and reprint requests to Dr. D.A. Lawlor, Department of Social Medicine, University of Bristol, Canynge Hall, Whiteladies Road, Bristol, BS8 2PR, U.K. E-mail: d.a.lawlor@bristol.ac.uk.

Received for publication 24 August 2002 and accepted in revised form 15 October 2002.

Abbreviations: HOMA, homeostasis model assessment.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

practitioner lists from 23 British towns. A total of 4,286 women (60% of those invited) participated, and baseline data were collected between April 1999 and March 2001. Ethics committee approval for the study was obtained, and full details of participants and measurements have been previously reported (18). Nearly all participants (99.8%) in the study were Caucasian.

Measurements

Participants were asked to provide details of their own birth weight and, for those with children, that of their first born offspring. Husbands' longest held occupation for married women and their own longest held occupation for single women were used to derive adult social class according to the Registrar General's standard classification (I, II, III nonmanual, III manual, IV, and V). Fathers' longest held occupation was used to derive childhood social class. Smoking was categorized as never, ex, or current at one of four levels: 1–9, 10–19, 20–29, or ≥30 cigarettes per day.

Standing and seated height were measured, without shoes, using a Harpenden Stadiometer recording to the nearest millimeter. Trunk length was calculated as the seated height minus the height of the stool. Leg length was taken as the standing height minus the trunk length. Weight was measured in light clothing without shoes to the nearest 0.1 kg using Soenhle portable scales. Waist circumference was measured at the midpoint between the lower rib and the iliac crest. Hip circumference was measured at the largest circumference below the waist. Two measurements of both waist and hip circumference were taken to the nearest millimeter using a flexible metal tape, and the mean of these two readings was used in all analyses.

Blood samples were taken after a 12-h fast. Insulin resistance was estimated according to the homeostasis model assessment (HOMA) as the product of fasting glucose (mmol/l) and insulin (μU/ml) divided by the constant 22.5 (19). HOMA scores were not calculated for women with a fasting glucose ≥8 mmol/l or those with a diagnosis of diabetes, as the results are inaccurate in these groups (19). Insulin was measured using an assay that does not cross-react with proinsulin (20). Total cholesterol, HDL cholesterol, and triglycerides were measured in serum samples using a Hitachi 747 analyzer (Roche Diagnostics) and standard reagents. A Dinamap 1846SX vital signs monitor was used to measure blood pressure. Arm circumference was measured and the appropriate cuff size used. Seated blood pressure was taken twice in succession with the right arm supported on a cushion, and the mean of the two measurements was used in all analyses.

Statistical analysis

The association between childhood and adult anthropometric measures was assessed using age-adjusted Pearson's partial correlation coefficients. Student's *t* test was used to compare age, insulin resistance, and other risk factors between those with details of birth weight and those without these data. Multiple linear regression was used to assess the independent associations of own birth weight, offspring birth weight, leg length, childhood social class, adult BMI, and waist-to-hip ratio with insulin resistance and other components of the insulin resistance syndrome (systolic blood pressure, HDL cholesterol, and triglyceride levels) after adjustment for potential confounding factors (age, adult social class, and smoking) and for each of the other early- and later-life factors. A likelihood ratio test was used to test for interactions between early life factors and adult obesity in the association with insulin resistance. HOMA scores and triglyceride levels were log normal: geometric means are presented, and the natural log of the levels were used in the regression models.

RESULTS — Of the 4,286 participants in the British Women's Heart Study (18), 1,419 provided details of their birth weight. Twenty-five women gave a birth weight that was ≥5.0 kg. These birth weights ranged from 5.45 to 6.42 kg. Although exclusion of these individuals from the analysis did not importantly alter any of our results, these birth weights are implausible and we have therefore restricted our analysis to the 1,394 (33% of the original cohort) women with self-reported birth weights ≤5.0 kg. The mean age of the women who provided birth weight data was 1.5 years younger than those who did not (67.9 vs. 69.4 years, $P < 0.001$). However, there were no differences in age-adjusted mean HOMA scores, systolic blood pressure, lipid measurements, BMI, or waist-to-hip ratio between women who provided details of their birth weight and those who did not (all *P* values >0.2). Table 1 shows the age-adjusted partial correlation coefficients between adult and childhood anthropometric measures. With further adjustment for BMI, the inverse association between birth weight and waist-to-hip ratio increased to −0.06 (95% CI −0.12 to −0.01).

Women in the lowest third of birth weight but highest third of adult BMI were the most insulin resistant (Fig. 1). For women in the lowest (16.89–25.16 kg/m^2) and middle thirds (25.17–28.77 kg/m^2) of adult BMI, there was very little independent (after adjustment for age, adult social class, smoking, offspring birth weight, leg length, childhood social class, and adult waist-to-hip ratio) association between birth weight and insulin resistance: −0.02 (95% CI −0.08 to 0.04) log HOMA score per 1-SD increase in own birth weight for the lowest third and −0.03 (−0.10 to 0.04) for the middle third. For women in the highest third of BMI (>28.77 kg/m^2), there was a strong independent association between low birth weight and insulin resistance: −0.12 (−0.19 to −0.04) (*P* for interaction = 0.04). There was no evidence of other interactions between any of the early life factors and either adult BMI or waist-to-hip ratio in any of the associations with insulin resistance or other components of the insulin resistance syndrome (all *P* values >0.40).

Table 2 shows the associations of early life factors with insulin resistance and components of the insulin resistance syndrome. For the fully adjusted model of insulin resistance on own birth weight, BMI was not included because of the interaction but waist-to-hip ratio, a measure of central obesity, was included. Own birth weight, offspring birth weight, and childhood social class were independently associated with insulin resistance. Fully adjusted (for confounding factors, each of the other early life factors, and adult general and central obesity) regression coefficients of logged HOMA score (insulin resistance) per 1 SD own birth weight were −0.06 (95% CI −0.10 to −0.02) per 1 SD offspring birth weight −0.05 (−0.09 to −0.01) and for the difference between nonmanual and manual childhood social class −0.07 (−0.14 to 0.00). Neither own nor offspring birth weight were associated with other com-

Table 1—*Partial age-adjusted Pearson's correlation coefficients between childhood and adulthood anthropometric measures*

	Own birth weight	Offspring birth weight	Adult weight	Adult BMI	Adult waist-to-hip ratio	Adult height	Adult leg length	Adult trunk length
Own birth weight	1							
Offspring birth weight	0.25 (0.19–0.31)	1						
Adult weight	0.11 (0.06–0.17)	0.15 (0.12–0.19)	1					
Adult BMI	0.02 (−0.04 to 0.08)	0.08 (0.04–0.12)	0.90 (0.88–0.91)	1				
Adult waist-to-hip ratio	−0.04 (−0.10 to 0.00)	0.02 (−0.02 to 0.05)	0.36 (0.33–0.39)	0.38 (0.35–0.41)	1			
Adult height	0.24 (0.18–0.30)	0.18 (0.14–0.22)	0.29 (0.24–0.32)	−0.13 (−0.16 to −0.10)	−0.04 (−0.07 to −0.01)	1		
Adult leg length	0.18 (0.13–0.24)	0.14 (0.11–0.18)	0.14 (0.11–0.17)	−0.23 (−0.26 to −0.20)	0.00 (−0.03 to 0.03)	0.80 (0.78–0.82)	1	
Adult trunk length	0.19 (0.13–0.25)	0.14 (0.10–0.18)	0.35 (0.32–0.38)	0.03 (0.00–0.07)	−0.07 (−0.10 to −0.04)	0.76 (0.74–0.79)	0.24 (0.21–0.27)	1

ponents of the insulin resistance syndrome. Women who were from manual social classes in childhood had adverse HDL cholesterol levels and triglyceride levels but did not have increased systolic blood pressure. Leg length was not associated with insulin resistance or other components of the insulin resistance syndrome after adjustment for adult obesity. Adjustment for BMI in the association between leg length and components of the insulin resistance syndrome may represent over adjustment since height is used to derive BMI and leg length is a component of height. When weight was used in place of BMI in the fully adjusted models, greater leg length was independently associated with reduced insulin resistance (−0.09 [0.12 to −0.06] log HOMA score per 1 SD leg length), lower levels of HDL cholesterol (0.06 [0.03–0.09] mmol/l per 1 SD leg length), and higher levels of triglycerides (−0.05 [−0.08 to −0.03] mmol/l per 1 SD leg length) but was not associated with systolic blood pressure.

Table 3 shows the associations of adult BMI and waist-to-hip ratio with insulin resistance and components of the insulin resistance syndrome. In age-adjusted models, increased levels of both measures of adult obesity were associated with increased insulin resistance, systolic blood pressure, and triglyceride levels and with reduced HDL levels. In the fully adjusted models, the association between BMI and systolic blood pressure was attenuated to the null, but all other associations remained. The associations between adult measures of obesity and insulin resistance were of a greater magnitude than those between early life factors and adult insulin resistance.

CONCLUSIONS — Low birth weight, low offspring birth weight, short leg length, manual childhood social class, high adult BMI, and greater adult waist-to-hip ratio were all independently asso-

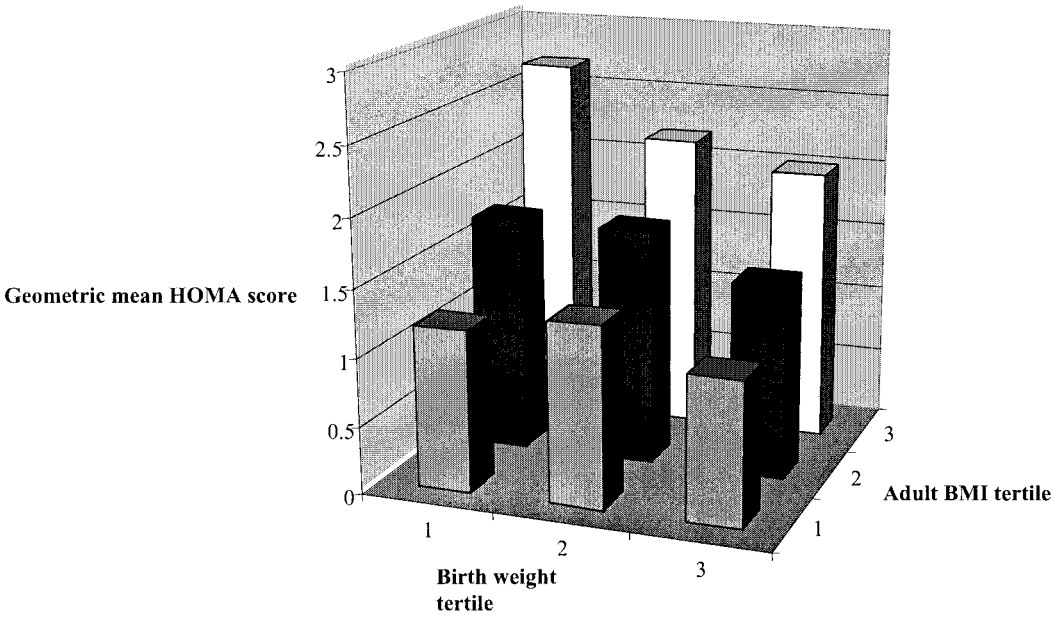

Figure 1—*Age-adjusted geometric means of insulin resistance (HOMA score) by tertiles of birth weight and adult BMI.*

Table 2—*Regression coefficient (95% CI) of insulin resistance and components of the insulin resistance syndrome per SD of own birth weight, offspring birth weight, leg length, and for the difference between nonmanual and manual childhood social class*

	Number with complete data on all covariates included in models	Covariates included in regression model			
		Age	Age, smoking, adult social class	Age, smoking, adult social class, and other early life factors*	Age, smoking, adult social class, other early life factors, and adult obesity†
Own birth weight					
HOMA score (logged)	870	−0.08 (−0.12 to −0.04)	−0.08 (−0.12 to −0.04)	−0.06 (−0.10 to −0.02)	−0.06 (−0.10 to −0.02)‡
Systolic blood pressure (mmHg)	1,039	−0.37 (−1.83 to 1.09)	−0.38 (−1.84 to 1.08)	−0.03 (−1.57 to 1.51)	−0.09 (−1.62 to 1.45)
HDL cholesterol (mmol/l)	1,005	0.02 (−0.01 to 0.05)	0.02 (−0.01 to 0.05)	0.00 (−0.03 to 0.03)	0.01 (−0.02 to 0.04)
Triglyceride (logged)	1,005	−0.03 (−0.05 to 0.00)	−0.03 (−0.05 to 0.00)	−0.02 (−0.05 to 0.02)	−0.02 (−0.05 to 0.01)
Offspring birth weight					
HOMA score (logged)	870	−0.06 (−0.10 to −0.01)	−0.06 (−0.10 to −0.01)	−0.03 (−0.07 to 0.00)	−0.05 (−0.09 to −0.01)
Systolic blood pressure (mmHg)	1,039	−1.07 (−2.52 to 0.39)	−1.13 (−2.59 to 0.32)	−1.11 (−2.64 to 0.40)	−1.06 (−2.58 to 0.46)
HDL cholesterol (mmol/l)	1,005	0.02 (−0.01 to 0.05)	0.02 (−0.01 to 0.05)	0.01 (−0.02 to 0.04)	0.02 (0.00 to 0.05)
Triglyceride (logged)	1,005	−0.01 (−0.04 to 0.02)	−0.01 (−0.04 to 0.22)	0.00 (−0.03 to 0.03)	0.00 (−0.03 to 0.03)
Leg length					
HOMA score (logged)	870	−0.08 (−0.12 to −0.04)	−0.08 (−0.12 to −0.04)	−0.06 (−0.10 to −0.03)	0.00 (−0.03 to 0.04)
Systolic blood pressure (mmHg)	1,039	−0.09 (−1.49 to 1.30)	−0.15 (−1.55 to 1.25)	−0.07 (−1.50 to 1.36)	0.14 (−1.33 to 1.62)
HDL cholesterol (mmol/l)	1,005	0.05 (0.03 to 0.08)	0.05 (0.03 to 0.08)	0.05 (0.02 to 0.08)	0.02 (−0.01 to 0.05)
Triglyceride (logged)	1,005	−0.05 (−0.08 to −0.03)	−0.05 (−0.08 to −0.02)	−0.05 (−0.08 to −0.02)	−0.02 (−0.05 to 0.00)
Childhood social class§					
HOMA score (logged)	870	−0.11 (−0.20 to −0.01)	−0.11 (−0.20 to −0.01)	−0.09 (−0.18 to −0.01)	−0.07 (−0.14 to 0.00)
Systolic blood pressure (mmHg)	1,039	−3.55 (−7.00 to −0.09)	−3.68 (−7.19 to −0.17)	−3.63 (−7.16 to −0.10)	−3.36 (−6.88 to 0.16)
HDL cholesterol (mmol/l)	1,005	0.13 (0.06–0.19)	0.12 (0.05–0.19)	0.11 (0.04–0.17)	0.08 (0.02–0.15)
Triglyceride (logged)	1,005	−0.10 (−0.17 to −0.03)	−0.09 (−0.16 to −0.02)	−0.08 (−0.15 to −0.01)	−0.06 (−0.12 to 0.00)

Own birth weight, 1 SD = 0.80 kg; offspring birth weight, 1 SD = 0.52 kg; leg length, 1 SD = 42.49 cm. *Other early life factors: simultaneous adjustment for all early life factors (own birth weight, offspring birth weight, leg length, and childhood social class). †Adult obesity: simultaneous adjustment for both adult BMI (general obesity) and waist-to-hip ratio (central obesity). ‡In these models for own birth weight, only waist-to-hip ratio was included in the association with insulin resistance because of the interaction with BMI. §Difference between nonmanual and manual social classes.

ciated with adult insulin resistance. There was an interaction between own birth weight and adult BMI in the association with insulin resistance, such that low birth weight only increased risk in those who were in the highest third of the distribution of BMI. Own birth weight and offspring birth weight were not associated with other components of the insulin resistance syndrome, whereas both shorter leg length and being from manual social classes in childhood were independently associated with adverse lipid profiles. Adult BMI and waist-to-hip ratio were both strongly and independently associated with insulin resistance and other components of the insulin resistance syndrome. These results suggest that genetic factors, intrauterine environment, early childhood environment, and adult environmental factors associated with obesity are all important in determining adult insulin resistance and emphasize the importance of taking a life course approach in studying the etiology of adult cardiovascular disease (21).

Although the association between offspring birth weight and insulin resistance may be due to maternal environmental factors rather than genetic factors (22), the findings in other studies of an association between offspring birth weight and fathers' diabetes and heart disease risk suggest that the transgenerational associations are, at least in part, related to genetic factors (13,14). Previous studies have not made adjustment for offspring birth weight in examining the association between birth weight and components of the insulin resistance syndrome. The inverse association between birth weight and insulin resistance in women in the highest third of birth weight remained even after adjustment for offspring birth weight and other early life factors, suggesting that genetic effects do not account for all of the association between birth weight and insulin resistance.

The interaction between birth weight and adult BMI is consistent with findings from other studies of a similar interaction in the association between birth size and BMI in the association with insulin resistance (23), type 2 diabetes (24), and coronary heart disease (25). One possible explanation is found in the "thrifty phenotype hypothesis," which suggests that poor intrauterine nutrition leads to increased peripheral muscle resistance to the action of insulin in the developing fe-

Table 3—*Regression coefficient (95% CI) of insulin resistance and components of the insulin resistance syndrome per SD of adult BMI and waist-to-hip ratio*

	Number with complete data on all covariates	Covariates included in regression model			
		Age	Age, smoking, adult social class	Age, smoking, adult social class, and other adult factors*	Age, smoking, adult social class, other adult factor, and early life factors†
BMI					
HOMA score (logged)	870	0.30 (0.26–0.34)	0.30 (0.27–0.34)	0.24 (0.20–0.28)	0.25 (0.20–0.29)
Systolic blood pressure (mmHg)	1,039	1.53 (0.04–3.01)	1.55 (0.06–3.04)	0.35 (−1.28 to 1.98)	0.53 (−1.17 to 2.23)
HDL cholesterol (mmol/l)	1,005	−0.15 (−0.17 to −0.12)	−0.15 (−0.17 to −0.12)	−0.11 (−0.14 to −0.08)	−0.11 (−0.14 to −0.08)
Triglyceride (logged)	1,005	0.14 (0.11–0.16)	0.14 (0.11–0.16)	0.08 (0.05–0.11)	0.08 (0.05–0.11)
Waist-to-hip ratio					
HOMA score (logged)	870	0.26 (0.21–0.28)	0.25 (0.21–0.29)	0.15 (0.11–0.19)	0.15 (0.11–0.19)
Systolic blood pressure (mmHg)	1,039	2.77 (1.35–4.19)	2.93 (1.49–4.36)	2.78 (1.20–4.37)	2.68 (1.09–4.27)
HDL cholesterol (mmol/l)	1,005	−0.13 (−0.16 to −0.10)	−0.13 (−0.16 to −0.10)	−0.08 (−0.11 to −0.05)	−0.08 (−0.11 to −0.05)
Triglyceride (logged)	1,005	0.14 (0.11–0.16)	0.14 (0.11–0.16)	0.08 (0.05–0.11)	0.08 (0.05–0.11)

BMI, 1 SD = 5.01 kg/m^2; waist-to-hip ratio, 1 SD = 0.069. *Other adult factors: BMI adjusted for waist-to-hip ratio and waist-to-hip ratio adjusted for BMI. †Early life factors: adjusted for own birth weight, offspring birth weight, leg length, and childhood social class.

tus so that energy (glucose) is preferentially diverted to essential organs, such as the brain (9). The fetus "programmed" for thrift then has an increased risk of insulin resistance and cardiovascular disease in later life if they become obese (9). Unlike some other studies (26), we found no association between birth weight and systolic blood pressure or between birth weight and lipid abnormalities. However, a recent systematic review and meta-analysis of the birth weight/blood pressure relationship suggested that this association may have been exaggerated in some studies because of inadequate adjustment for potential confounding factors and publication bias (27). Not all studies have shown an inverse association between birth weight and blood pressure or adverse lipid profiles (23,27).

The more consistent associations between leg length and childhood social class and other components of the insulin resistance syndrome suggest that postnatal environmental factors may be more important early life determinants of the insulin resistance syndrome than intrauterine environmental factors. Alternatively increasing evidence suggests that adverse environmental exposures at different times in early life (both intrauterine and postnatal) have differential effects on different aspects of the insulin resistance syndrome (28). Leg length is an indicator of childhood nutrition, in particular infant nutrition (6), suggesting that its independent association with insulin resistance and adverse lipid profiles may be due specifically to early dietary intake rather than to a broader childhood social class effect.

The strongest and most consistent associations with all components of the insulin resistance syndrome were found for adult measures of obesity, perhaps suggesting that public health interventions to reduce insulin resistance might be best undertaken in adulthood. However, adult obesity is itself determined by early life factors, in particular postnatal childhood growth and infant feeding (29–31). The independent associations of early life factors, even after adjustment for adult obesity, suggest that early life factors influence adult insulin resistance directly rather than through an effect on adult obesity only. Interventions to reduce obesity in adulthood have limited long-term impact (32), and preventing the development of adult obesity and insulin resistance by attention to early life factors may be a more effective means of reducing adult cardiovascular disease, although to date there are no intervention studies in childhood with outcomes measured in adult life.

Study limitations

We used self-report of birth weight and offspring birth weight. Self-report of birth weight in adults is moderately correlated with hospital records (33). Correlations between self-report of birth weight and anthropometric measures in the women in this study were of the magnitude expected from previous studies in which medically recorded birth weights have been used (8). Women in our study were born between 1929 and 1940, and the mean (±SD) self-reported birth weight for these women was 3.28 ± 0.80 kg, which is consistent with hospital records of women born between 1923 and 1930 in Hertfordshire (3.42 kg) (4) as well as with women in the 1946 British cohort (3.32 ± 0.49 kg; Dr. D. Kuh, personal communication). Only one-third of the women in our study provided data on their own birth weight and were slightly younger than those who did not provide this information. There were no differences between those providing birth weight data and those who did not with respect to levels of insulin resistance or other components of the insulin resistance syndrome. Misclassification bias or selection bias resulting from self-report of birth weight are therefore unlikely to explain our results. Maternal report of offspring birth weight is likely to be accurate (34), and 94% of the women with offspring, in our total cohort, provided these data (11). Data on childhood social class, based on father's occupation, was available for 86% of all the women in the cohort (16). Our study population is ethnically homogeneous, which means that the results are not confounded by differences in leg length and insulin resistance among various ethnic groups but

that the results may not necessarily be generalizable to other ethnic groups.

Implications

This is the first study to examine the independent associations of a broad range of early life factors and adult obesity with insulin resistance. Insulin resistance is an important risk factor for coronary heart disease and is a major mediating factor in the associations between early life factors and coronary heart disease. Our results suggest that genetic factors, intrauterine environment, and early childhood and adult environmental factors are all relevant in determining adult insulin resistance. As both insulin resistance and obesity have their roots in early life experiences, public health initiatives for the control of cardiovascular disease that tend to emphasize intervention in adult life require some reorientation toward early life. Long-term follow-up of pregnancy diet supplementation trials (35), maternal financial and social support studies (36), and childhood nutritional intervention studies (37) may shed further light on the causal nature of the relationships observed in this study.

Acknowledgments— The British Women's Heart and Health Study is funded by the Department of Health. D.A.L. is funded by a Medical Research Council (MRC)/Department of Health training fellowship. The views expressed in this publication are those of the authors and not necessarily those of the Department of Health or MRC.

The British Women's Heart & Health Study is codirected by S.E., Professor Peter Whincup, Dr. Goya Wannamethee, and D.A.L. We thank Carol Bedford, Alison Emerton, Nicola Frecknall, Karen Jones, Mark Taylor, and Katherine Wornell for collecting and entering data; all of the general practitioners and their staff who helped with data collection; and the women who participated in the study.

All authors developed the study aim and design. D.A.L. undertook the initial analysis and coordinated writing of the manuscript. All authors contributed to the final version. D.A.L. acts as guarantor for the report.

References

1. Enos MWF, Holmes LCRH, Beyer CJ: Coronary disease among United States soldiers killed in action in Korea. *JAMA* 152:1090–1093, 1953
2. McNamara JJ, Molot MA, Stremple JF, Cutting RT: Coronary artery disease in combat casualties in Vietnam. *JAMA* 216: 1185–1187, 1971
3. Barker DJP: *Mothers, Babies and Health in Later Life*. London, Churchill Livingstone, 1998
4. Fall CH, Osmond C, Barker DJ, Clark PM, Hales CN, Stirling Y, Meade TW: Fetal and infant growth and cardiovascular risk factors in women. *BMJ* 310:428–432, 1995
5. Davey Smith G, Hart C, Blane D, Hole D: Adverse socioeconomic conditions in childhood and cause specific adult mortality: prospective observational study. *BMJ* 316:1631–1635, 1998
6. Wadsworth MEJ, Hardy RJ, Paul AA, Marshall SF, Cole TJ: Leg and trunk length at 43 years in relation to childhood health, diet and family circumstances: evidence from the 1946 national birth cohort. *Int J Epidemiol* 31:383–390, 2002
7. Davey Smith G, Greenwood R, Gunnell D, Sweetnam P, Yarnell J, Elwood P: Leg length, insulin resistance, and coronary heart disease risk: the Caerphilly Study. *J Epidemiol Community Health* 55:867–872, 2001
8. Lawlor DA, Ebrahim S, Davey Smith G: The association between components of adult height and type II diabetes and insulin resistance: British Women's Heart and Health Study. *Diabetologia* 45:1097–1106, 2002
9. Hales CN, Barker DJP: The thrifty phenotype hypothesis. *Br Med Bull* 60:5–20, 2001
10. Hattersley AT, Tooke JE: The fetal insulin hypothesis: an alternative explanation of the association of low birthweight with diabetes and vascular disease. *Lancet* 353: 1789–1792, 1999
11. Lawlor DA, Davey Smith G, Ebrahim S: Birth weight of offspring and insulin resistance in late adulthood: cross sectional survey using data from the British Women's Heart and Health Study. *BMJ* 325: 359–362, 2002
12. Davey Smith G, Hart C, Ferrell C, Upton M, Hole D, Hawthorne V, Watt G: Birth weight of offspring and mortality in the Renfrew and Paisley study: prospective observational study. *BMJ* 315:1189–1193, 1997
13. Rasmussen F, Davey Smith G, Sterne J, Tynelius P, Leon DA: Birth characteristics of offspring and parental diabetes. *Am J Epidemiol* 153 (Suppl.):S47, 2001
14. Rasmussen F, Sterne JAC, Davey Smith G, Tynelius P, Leon DA: Fetal growth is associated with parents' cardiovascular mortality. *Am J Epidemiol* 153 (Suppl.): S98, 2001
15. Leitch I: Growth and health. *Br J Nutr* 5:142–151, 1951
16. Lawlor DA, Ebrahim S, Davey Smith G: Socioeconomic position in childhood and adulthood and insulin resistance: cross sectional survey using data from British women's heart and health study. *BMJ* 325: 805–807, 2002
17. Liese AD, Mayer-Davis EJ, Haffner SM: Development of the multiple metabolic syndrome: an epidemiologic perspective. *Epidemiol Rev* 20:157–172, 1998
18. Lawlor DA, Bedford C, Taylor M, Ebrahim S: Geographic variation in cardiovascular disease, risk factors and their control in older women: British Women's Heart and Health Study. *J Epidemiol Community Health*. In press
19. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412–419, 1985
20. Andersen L, Dinesen B, Jorgensen PN, Poulsen F, Roder ME: Enzyme immunoassay for intact human insulin in serum or plasma. *Clin Chem* 39:578–582, 1993
21. Lawlor DA, Ebrahim S, Davey Smith G: A lifecourse approach to cardiovascular health: coronary heart disease and stroke. In *Lifecourse Influences on Women's Health*. Kuh D, Hardy R, Eds. Oxford, U.K., Oxford University Press, 2002, p. 86–120
22. Lawlor DA, Davey Smith G, Ebrahim S: Association between leg-length and offspring birthweight: partial explanation for the trans-generational associations between birthweight and cardiovascular disease: findings from the British Women's Heart and Health Study. *Paediatr Perinat Epidemiol*. In press
23. Lithell HO, McKeigue PM, Berglund L, Mohsen R, Lithell U-B, Leon DA: Relation of size at birth to non-insulin dependent diabetes and insulin concentrations in men aged 50–60 years. *BMJ* 312:406–410, 1996
24. Rich-Rich-Edwards JW, Colditz GA, Stampfer MJ, Willett WC, Gillman MW, Hennekens CH, Speizer FE, Manson JE: Birthweight and the risk for type 2 diabetes mellitus in adult women. *Ann Intern Med* 130:278–284, 1999
25. Frankel S, Elwood P, Sweetnam P, Yarnell J: Birth weight, body mass index in middle age, and incident coronary heart disease. *Lancet* 348:1478–1480, 1996
26. Huxley RR, Shiell AW, Law CA: The role of size at birth and post-natal catch-up growth in determining systolic blood pressure: a systematic review of the literature. *J Hyperten* 18:815–831, 2000
27. Huxley R, Neil A, Collins R: Unravelling the "fetal origins" hypothesis: is there really an inverse association between birth weight and future blood pressure? *Lancet* 360:659–665, 2002
28. McKeigue P: Diabetes and insulin action. In *A Life Course Approach to Chronic Dis-*

ease Epidemiology. Kuh D, Ben-Shlomo Y, Eds. 2nd ed. Oxford, U.K., Oxford University Press. In press
29. Parsons TJ, Power C, Logan S, Summerbell CD: Childhood predictors of adult obesity: a systematic review. *Int J Obes* 23: S1–S107, 1999
30. Parsons TJ, Power C, Manor O: Fetal and early life growth and body mass index from birth to early adulthood in 1958 British cohort: longitudinal study. *BMJ* 323:1331–1335, 2001
31. Gillman MW, Rifas-Shiman SL, Camargo CA Jr, Berkey CS, Frazier AL, Rockett HR, Field AE, Colditz GA: Risk of overweight among adolescents who were breastfed as infants. *JAMA* 285:2461–2467, 2001
32. Yanovski SZ, Yanovski JA: Obesity. *N Engl J Med* 346:591–602, 2002
33. Kemp M, Gunnell D, Maynard M, Davey Smith G, Frankel S: How accurate is self reported birth weight among the elderly? *J Epidemiol Community Health* 54:639–640, 2000
34. O'Sullivan JJ, Pearce MS, Parker L: Parental recall of birth weight: how accurate is it? *Arch Dis Child* 82:202–203, 2000
35. de Onis M, Villar J, Glumezoglu M: Nutritional interventions to prevent intrauterine growth retardation: evidence from randomized controlled trials. *Euro J Clin Nutr* 52 (Suppl.):S83–S93, 1998
36. Spencer B, Thomas H, Morris J: A randomized controlled trial of the provision of a social support service during pregnancy: the South Manchester Family Worker Project. *Br J Obstet Gynaecol* 96: 281–288, 1989
37. Gunnell D, Davey Smith G, Ness F, Frankel S: The effects of dietary supplementation on growth and adult mortality: a re-analysis and follow-up of a prewar study. *Public Health* 114:109–116, 2000