Cardiorespiratory Fitness and Vigorous Leisure-Time Physical Activity Modify the Association of Small Size at Birth With the Metabolic Syndrome

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OBJECTIVE — Small size at birth has been associated with components of the metabolic syndrome, but little is known about the association with the metabolic syndrome itself or whether leisure-time physical activity (LTPA) and cardiorespiratory fitness modify that association. We studied the association of size at birth with the metabolic syndrome.

RESEARCH DESIGN AND METHODS — Birth weight and length, the metabolic syndrome (World Health Organization criteria), LTPA over the previous 12 months, and Vo_{2max} were assessed in 462 nondiabetic middle-aged Finnish men who were part of a population-based cohort study.

RESULTS — Men with a ponderal index (kg/m^3) at birth in the lower third had higher fasting insulin and glucose levels than men in the upper third in age-adjusted analyses and were at least twofold more likely to have the metabolic syndrome, even in men without cardiovascular disease. Adjustment for childhood or adult socioeconomic status or adult BMI did not attenuate the association. Thinness at birth was even more clearly associated with hyperinsulinemia and the metabolic syndrome in men engaging in <25 min/wk of vigorous LTPA and in men with a Vo_{2max} <28.6 ml · kg^{-1} · min^{-1} or <2.44 l/min. In active and fit men, however, the association was absent.

CONCLUSIONS — Small size at birth was associated with the metabolic syndrome in middle-aged men already before development of diabetes or cardiovascular disease. Thinness at birth may carry with it lifelong metabolic consequences, but regular strenuous physical activity and maintenance of cardiorespiratory fitness may alleviate or eliminate those consequences.

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Although the precise pathophysiology of the metabolic syndrome remains unclear, direct and indirect evidence indicates that largely environmental factors such as sedentary lifestyle, diet, and thinness at birth or low birth weight play an important role (1–6). Many studies have shown an association of small size at birth with components of or diseases related to the metabolic syndrome, including diabetes, coronary heart disease, insulin resistance, glucose intolerance, hypertension (7–13), and, less consistently, dyslipidemia and an abdominal fat distribution (11). Several studies have shown an association of small size at birth with the metabolic syndrome itself (9,14,15), but these studies have used definitions devised by the authors themselves. Based on these associations of low birth weight that extend well into the normal range, it has even been suggested that the metabolic syndrome should be called the "small-baby" syndrome (14).

These studies have given rise to the thrifty phenotype hypothesis (2,16,17). In utero undernourishment, reflected as reduced growth, brings about permanent adaptations in structure, metabolism, and endocrine function in the fetus. These adaptations are advantageous in the short term, but deleterious in the long term. Reduced fetal growth and consequent low birth weight, or more specifically thinness at birth, is believed to be largely a consequence of the fetal environment, but genetic factors may also be important (18).

The metabolic syndrome is a concurrence of usually mild and varying degrees of disturbed glucose and insulin metabolism, overweight and abdominal fat distribution, dyslipidemia, and hypertension (1,3). Because of the lack of accepted definitions of the metabolic syndrome in the past, most studies have focused on individual components rather than the metabolic syndrome itself. We have recently validated the World Health Organization (WHO) definition (19) of the metabolic syndrome in the prediction of prevalent and incident diabetes during middle age (20). This definition also predicted increased cardiovascular and overall mortality even in men initially without diabetes and cardiovascular disease (CVD) (20). Indeed, the importance of

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Abbreviations: CVD, cardiovascular disease; KIHD, Kuopio Ischemic Heart Disease Risk Factor Study; LTPA, leisure-time physical activity; MET, metabolic equivalent; WHO, World Health Organization.

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

Table 1—*Characteristics of 462 middle-aged men with and without the metabolic syndrome*

	Without metabolic syndrome	With metabolic syndrome	*P*
n	379	83	
Age (years)	50.4 ± 6.4	51.6 ± 6.4	0.080
Childhood socioeconomic status*	1.9 ± 0.8	1.9 ± 0.7	0.54
Score for adult socioeconomic status†	8.0 ± 4.1	7.8 ± 4.4	0.62
Current smoker (%)	30.6	32.5	0.70
Blood pressure (mmHg)	131 ± 15/88 ± 10	140 ± 16/93 ± 9.1	<0.001
Hypertension (%)	50.4	90.4	<0.001
Blood pressure medication (%)	15.3	43.4	<0.001
Cardiovascular disease (%)	28.4	46.3	<0.001
BMI (kg/m^2)	26.1 ± 2.9	29.6 ± 3.2	<0.001
Waist-to-hip ratio	0.94 ± 0.06	0.99 ± 0.04	<0.001
Insulin sensitivity index	0.50 ± 0.05	0.43 ± 0.03	<0.001
Fasting serum insulin (mU/l)	8.8 (6.9–10.9)	16.8 (14.4–21.5)	<0.001
Fasting blood glucose (mmol/l)	4.49 ± 0.45	4.91 ± 0.53	<0.001
Impaired fasting glycemia (%)	1.3	15.9	<0.001
LDL cholesterol (mmol/l)	3.90 ± 0.96	3.78 ± 0.92	0.13
HDL cholesterol (mmol/l)	1.34 ± 0.29	1.15 ± 0.25	<0.001
Serum triglycerides (mmol/l)	1.03 (0.76–1.42)	1.82 (1.30–2.43)	<0.001
Maximal oxygen uptake (ml · kg^{-1} · min^{-1})	33.4 ± 8.1	26.4 ± 6.2	<0.001
Vigorous LTPA (min/week)	24 (5–79)	14 (0–43)	0.13
Birth weight (g)	3,563 ± 520	3,486 ± 506	0.21
Birth length (cm)	50.4 ± 1.9	50.5 ± 1.4	0.69
Ponderal index at birth (kg/m^3)	27.9 ± 4.3	27.0 ± 3.2	0.075

Data are means ± SD or median (interquartile range) unless otherwise indicated. *Three classifications from 1 to 3, a low score indicates low childhood socioeconomic status; †a low score indicates high socioeconomic status.

the metabolic syndrome from a clinical and public health standpoint is in its early stages, before development of diabetes or CVD.

We have recently shown that middle-aged men who are fit or who engage in regular, and especially vigorous, leisure-time physical activity (LTPA) are less likely to develop the metabolic syndrome than their sedentary counterparts (6). Although improved prenatal care might hypothetically decrease the deleterious consequences during adulthood of thinness at birth, it would be of obvious interest and importance from a public health perspective to know what lifestyle factors might mitigate the metabolic consequences of thinness at birth. We are not aware of any studies that have been published regarding the possible modifying role of LTPA or fitness on the association of low birth weight or thinness at birth with the metabolic syndrome during adulthood.

We evaluated the association of thinness at birth and low birth weight with the metabolic syndrome in a population-based cohort of middle-aged men, using a modified WHO definition (20). We also assessed whether the association of thinness at birth with the metabolic syndrome may be modified by LTPA or cardiorespiratory fitness by stratifying the men based on levels of current habitual physical activity or fitness.

RESEARCH DESIGN AND METHODS

Participants

The Kuopio Ischemic Heart Disease Risk Factor Study (KIHD) is a prospective population-based study (22). The original study population comprised a random age-stratified sample of 2,682 men living in eastern Finland who were 42, 48, 54, or 60 years of age at baseline. The University of Kuopio Research Ethics Committee approved the study. All participants gave their written informed consent.

Data on birth weight and length were available for 624 men. Data were missing for many men who were born in the area of Eastern Finland annexed by the Soviet Union at the end of World War II. Many records were destroyed during the war or in fires or were lost for other reasons. Some men were born at home without the assistance of a midwife, nurse, or physician. Of the 624 men, complete data for defining the metabolic syndrome were available for 462. Men for whom birth data were available were younger (50.6 ± 6.0 years) than men with missing birth data (53.9 ± 4.4 years). After adjusting for age, men with complete birth data did not differ significantly from men with missing data in any of the clinical, biochemical, or anthropometric data shown in Table 1.

Assessment of data on birth weight and length

For the present study, data on birth weight recorded in grams and length recorded in centimeters were collected in 1998–1999 from prenatal and pediatric health clinic and school records obtained from the community health center, hospital, and home. The ponderal index was calculated as birth weight (kg)/length (m^3).

Assessment of components of the metabolic syndrome

Blood pressure was measured with a random-zero mercury sphygmomanometer

(Hawksley, U.K.). Three measurements were recorded at 5-min intervals while the patient was supine, one measurement was recorded while standing, and two measurements were recorded while sitting. The mean of all six measurements was used as the systolic and diastolic blood pressure.

BMI was computed as weight divided by height squared. Waist circumference was calculated as the average of two measurements recorded after inspiration and after expiration (mean difference ≅1.5 cm) at the midpoint between the lowest rib and the iliac crest. The waist-to-hip ratio was defined as waist girth divided by hip circumference measured at the trochanter major.

Participants were asked to fast and to refrain from smoking for 12 h and to avoid alcohol intake for 3 days before blood sampling. Blood glucose was measured using a glucose dehydrogenase method. The serum samples for insulin determination were stored at −80°C and later analyzed with a Novo Biolabs radioimmunoassay kit (Novo Nordisk, Bagsvaerd, Denmark). LDL and HDL fractions were separated from fresh serum by ultracentrifugation and precipitation. LDL and HDL cholesterol and triglycerides were measured enzymatically.

Metabolic syndrome

The metabolic syndrome for men, according to the WHO definition, was modified for epidemiological studies in part as proposed by the European Group for the Study of Insulin Resistance (23) and defined as insulin resistance in the top 25% of the nondiabetic population, impaired fasting glycemia or diabetes, and presence of at least two of the following: abdominal obesity, dyslipidemia (triglycerides ≥1.70 or HDL <0.9 mmol/l), or hypertension (blood pressure ≥140/90 mmHg or use of blood pressure medication) (19).

Insulin resistance was estimated using a validated insulin sensitivity index (QUICKI) (24). The 25% cutoff was determined from the entire nondiabetic KIHD cohort for whom information on the core components of the metabolic syndrome was available. Impaired fasting glycemia was defined as fasting blood glucose level of 5.6–6.0 mmol/l (19). Diabetes was defined as fasting blood glucose level ≥6.1 mmol/l or a clinical diagnosis of diabetes with either dietary, oral medication, or insulin treatment (19). Men with diabetes were excluded from the study. The original WHO definition of low HDL cholesterol (<0.9 mmol/l) and abdominal obesity (waist-to-hip ratio >0.90 or BMI ≥30 kg/m^2) was maintained. As suggested by the European Group for the Study of Insulin Resistance, microalbuminuria was not included in the definition (21). This modified definition has been validated previously (20).

Assessment of childhood and adult economic status

We assessed childhood socioeconomic status with a three-category composite index (low, medium, or high) based on parents' education and occupation during the subject's childhood, whether the family lived on a farm, and whether the family was perceived as wealthy (25). Adult socioeconomic status was assessed with a composite index based on education and occupation, income, material wealth, and perception of financial security (25).

Assessment of LTPA

The validated KIHD 12-month Leisure-Time Physical Activity Questionnaire was used as described previously (24,25). This is a detailed quantitative questionnaire assessing the duration, frequency, and mean intensity of the most common lifestyle and structured LTPA of middle-aged Finnish men as recalled over the previous 12 months. The cutoff of ≥7.5 metabolic equivalents (METs; 1 MET is the metabolic expenditure at rest, corresponding to an oxygen uptake of 3.5 ml O_2/kg) for high-intensity physical activity included lifestyle and conditioning activities commonly considered vigorous (e.g., chopping wood or shoveling snow, skiing, jogging, ball sports) at the subjective intensities at which they were practiced (6). Low-intensity LTPA was defined as <4.5 METs. Moderate- and high-intensity LTPA was defined as ≥4.5 METs. The durations of LTPA were calculated in min/week.

Assessment of cardiorespiratory fitness

A graded symptom-limited maximal exercise test was performed on an electrically braked cycle ergometer (model 400L; Medical Fitness Equipment, Mearn, the Netherlands). $V_{O_{2max}}$ was measured directly with breath-by-breath respiratory gas exchange analysis (Medical Graphics 2001; Medical Graphics, St. Paul, Minnesota), as described previously (26,27).

Other assessments

Assessment of medical history, medication use, family history of diseases, and smoking (28) has been described previously.

Statistical analysis

Differences in anthropometric, biochemical, and clinical variables between men with and without the metabolic syndrome were assessed with the Student's *t* test or the χ^2 test as indicated. The age-adjusted associations of birth weight or ponderal index categories with insulin and glucose levels in middle age were assessed with ANCOVA, and the trend was analyzed with linear regression. The association of birth weight or ponderal index categories with the metabolic syndrome was estimated using logistic regression, with forced adjustment for age, and in separate models, adjustment for childhood socioeconomic status, adult socioeconomic status, and adult BMI. Indexes of birth weight and ponderal index were categorized into thirds for both logistic regression and covariate analyses. We also assessed whether the association of the ponderal index with insulin and glucose levels and the metabolic syndrome in middle age was modified by LTPA or cardiorespiratory fitness. For these analyses, we stratified the men by the weekly duration of median LTPA and cardiorespiratory fitness. Because especially $V_{O_{2max}}$ is strongly and inversely associated with age, we adjusted $V_{O_{2max}}$ and duration of vigorous LTPA for age (using the entire nondiabetic KIHD cohort for whom all variables for calculation of the metabolic syndrome were available) before determining cutoffs for stratification of $V_{O_{2max}}$ and vigorous LTPA. For $V_{O_{2max}}$ in ml · kg^{-1} · min^{-1}, we used a lower cutoff (40%) because so few cases (n = 11) of the metabolic syndrome were present in fit men when using median fitness as a cutoff. In stratified analyses, the ponderal index was dichotomized at the lower tertile for the statistical analyses. We also tested for the statistical interaction of physical activity and fitness with thinness at birth in the ANCOVA and logistic regression modes, including age and dichotomized measures of either physical activity or fitness, the ponderal index, and the appropriate product term. Triglyceride and insulin concentrations were

Table 2—*Age-adjusted association of the ponderal index and body weight at birth categorized into thirds with fasting serum insulin and blood glucose levels and insulin sensitivity*

Ponderal index categories	Insulin, glucose, and index values	Birth weight categories	Insulin, glucose, and index values
Fasting serum insulin levels (mU/l)			
<26.31 kg/m^3	12.0 (11.0–13.0)	<3,400 g	12.0 (11.0–13.0)
26.31–27.72 kg/m^3	10.5 (9.4–11.6)	3,400–3,780 g	10.5 (9.5–11.6)
>27.72 kg/m^3	10.3 (9.3–11.3)	>3,780 g	10.3 (9.2–11.3)
P value for effect	0.036	*P* value for effect	0.034
P value for trend	0.018	*P* value for trend	0.005
Fasting blood glucose levels (mmol/l)			
<26.31 kg/m^3	4.68 (4.60–4.76) mg/dl, 84.3	<3,400 g	4.68 (4.60–4.76) mg/dl, 84.3
26.31–27.72 kg/m^3	4.56 (4.48–4.65) mg/dl, 82.2	3,400–3,780 g	4.55 (4.47–4.63) mg/dl, 82.0
>27.72 kg/m^3	4.50 (4.42–4.58) mg/dl, 81.1	>3,780 g	4.50 (4.42–4.58) mg/dl, 81.1
P value for effect	0.005	*P* value for effect	0.004
P value for trend	0.001	*P* value for trend	0.004
Insulin sensitivity index			
<26.31 kg/m^3	0.483 (0.473–0.492)	<3,400 g	0.481 (0.472–0.490)
26.31–27.72 kg/m^3	0.495 (0.485–0.505)	3,400–3,780 g	0.495 (0.486–0.505)
>27.72 kg/m^3	0.500 (0.491–0.510)	>3,780 g	0.502 (0.493–0.511)
P value for effect	0.021	*P* value for effect	0.002
P value for trend	0.008	*P* value for trend	<0.001

Data are means (95% CI).

corrected for skewing using log transformation but are presented using untransformed values. Data are presented as means ± SD, medians, and interquartile ranges or simple percentages where appropriate in Table 1. Significance was considered to be $P < 0.05$. All statistical analyses were performed with SPSS 11.0 for Windows (Chicago, IL).

RESULTS — Men with the metabolic syndrome had a higher BMI and waist-to-hip ratio, higher serum triglyceride level and lower serum HDL level, higher fasting blood glucose and serum insulin levels, and higher blood pressure than men without the syndrome (Table 1). Moreover, men with the metabolic syndrome were older and more likely to have CVD or use blood pressure medication. Men without the metabolic syndrome had a much higher $V_{O_{2max}}$ and tended to engage in more vigorous LTPA (Table 1).

Association of the ponderal index and birth weight with fasting insulin and glucose concentrations and insulin sensitivity

After adjustment for age, men in the lower third of the ponderal index or birth weight had clearly higher insulin and glucose concentrations than men in the upper third (Table 2). A ponderal index or birth weight in the lower third was also associated with lower insulin sensitivity in middle age.

Association of the ponderal index and birth weight with the metabolic syndrome

In age-adjusted analyses, men with a ponderal index or body weight in the lower third at birth were roughly two times more likely to have the metabolic syndrome (Table 3). Adjustment for childhood socioeconomic status or adult socioeconomic status did not affect the association. Adjustment for BMI in middle age seemed to increase the association somewhat. Adjustment for adult height did not affect the association (not shown).

Association of the ponderal index and birth weight with the metabolic syndrome in men without CVD

In the 314 men without CVD, men with a low ponderal index were nearly three times more likely to have the metabolic syndrome (odds ratio [OR] 2.91 for the upper versus lower third, 95% CI 1.18–7.15). Similarly, men with a birth weight in the lowest third were also more likely to have the metabolic syndrome (OR 2.31 for the upper versus lower third, 95% CI 0.99–5.37).

Association of thinness at birth with vigorous LTPA and cardiorespiratory fitness

Thinness at birth was not associated with cardiorespiratory fitness (for the trend across tertiles of the ponderal index, $P = 0.65$) or duration of strenuous LTPA (for the trend across tertiles of the ponderal index, $P = 0.47$) in middle age.

Influence of vigorous LTPA and cardiorespiratory fitness on the association of thinness at birth with the metabolic syndrome

When stratifying the men by median weekly duration of vigorous LTPA, the association of the ponderal index at birth with insulin and glucose levels and the insulin sensitivity index was absent in men engaging in at least 25 min/week of strenuous LTPA (Table 4). In contrast, in more sedentary men, the association of the ponderal index with hyperinsulinemia was enhanced ($P = 0.033$ for the

Table 3—*ORs (95% CI) of the metabolic syndrome according to the ponderal index or body weight at birth with the metabolic syndrome in 462 middle-aged men*

Categories	Model 1*	Model 2†	Model 3‡	Model 4§
Ponderal index				
>27.72 kg/m^3	1	1	1	1
26.31–27.72 kg/m^3	1.60 (0.84–3.02)	1.25 (0.66–2.36)	1.62 (0.85–3.07)	1.82 (0.90–3.70)
<26.31 kg/m^3	2.19 (1.20–4.02)	2.21 (1.20–4.05)	2.25 (1.23–4.14)	2.57 (1.30–5.11)
Trend (*P*)	0.040	0.039	0.033	0.026
Birthweight				
>3,780 g	1	1	1	1
3,400–3,780 g	1.26 (0.67–2.37)	1.25 (0.66–2.36)	1.24 (0.66–2.34)	1.50 (0.74–3.05)
<3,400 g	1.98 (1.09–3.60)	2.02 (1.11–3.66)	2.02 (1.11–3.68)	2.70 (1.37–5.34)
Trend (*P*)	0.063	0.055	0.033	0.014

Data are means (95% CI). *Model 1: adjusted for age; †model 2: adjusted for age and childhood socioeconomic status; ‡model 3: adjusted for age and adult socioeconomic status; §model 4: adjusted for age and adult BMI.

interaction of vigorous physical activity and the ponderal index at birth), although the effects of stratification by duration of physical activity on the association with glucose levels ($P = 0.33$ for the interaction) and the insulin sensitivity index ($P = 0.50$ for the interaction) were less marked.

Similarly, the association of the ponderal index at birth with the metabolic syndrome in middle age was attenuated and no longer significant in men engaging in at least 25 min/week of strenuous leisure-time activity (Fig. 1*A*). In sedentary men, however, the association of the ponderal index with metabolic syndrome was even clearer. In statistical testing, however, the multiplicative interaction of vigorous physical activity and the ponderal index at birth was not significant ($P = 0.39$). The duration of total, low-intensity, and moderate-intensity LTPA did not clearly modify the association.

Likewise, the association of the ponderal index with insulin levels ($P = 0.009$ for the interaction between thinness at birth and $V_{O_{2max}}$), and glucose levels ($P = 0.020$ for the interaction), and the insulin sensitivity index ($P = 0.15$ for the interaction) in more fit men was absent, whereas the association was

Table 4—*Age-adjusted association of the ponderal index at birth categorized into thirds with fasting serum insulin and blood glucose levels and insulin sensitivity, stratified by duration of vigorous LTPA*

Ponderal index categories	Vigorous LTPA <25 min/week ($n = 133$)	Vigorous LTPA ≥25 min/week ($n = 134$)
Fasting serum insulin levels (mU/l)		
<26.31 kg/m^3	14.3 (12.1–16.5)	10.5 (8.9–12.0)
26.31–27.72 kg/m^3	9.8 (7.6–12.0)	10.3 (8.5–12.1)
>27.72 kg/m^3	10.4 (8.4–12.4)	9.5 (7.8–11.2)
P value, lowest versus upper two thirds	0.002	0.56
P for the interaction between physical activity and thinness at birth	0.033	
Fasting blood glucose levels (mmol/l)		
<26.31 kg/m^3	4.70 (4.54–4.85) mg/dl, 84.7	4.50 (4.37–4.63) mg/dl, 81.1
26.31–27.72 kg/m^3	4.54 (4.39–4.70) mg/dl, 81.8	4.45 (4.29–4.60) mg/dl, 81.2
>27.72 kg/m^3	4.51 (4.36–4.65) mg/dl, 81.3	4.54 (4.39–4.68) mg/dl, 81.8
P value, lowest versus upper two-thirds	0.15	0.94
P for the interaction between physical activity and thinness at birth	0.33	
Insulin sensitivity index		
<26.31 kg/m^3	0.474 (0.455–0.493)	0.492 (0.476–0.507)
26.31–27.72 kg/m^3	0.496 (0.477–0.515)	0.503 (0.484–0.521)
>27.72 kg/m^3	0.496 (0.479–0.513)	0.504 (0.487–0.521)
P value, lowest versus upper two-thirds	0.049	0.22
P for the interaction between physical activity and thinness at birth	0.50	

Data are means (95% CI).

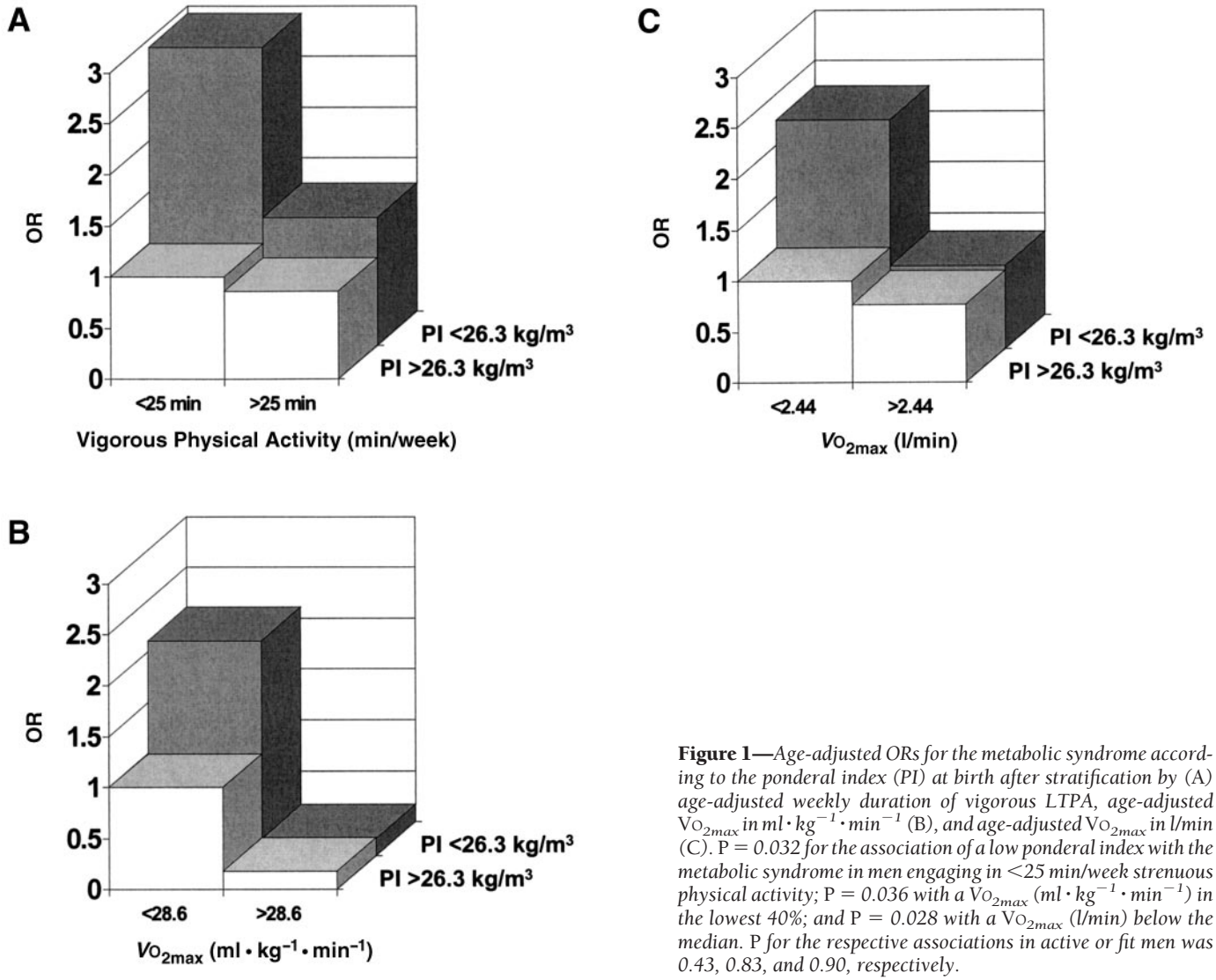

Figure 1—*Age-adjusted ORs for the metabolic syndrome according to the ponderal index (PI) at birth after stratification by* (A) *age-adjusted weekly duration of vigorous LTPA, age-adjusted* $\dot{V}O_{2max}$ *in ml · kg^{-1} · min^{-1}* (B)*, and age-adjusted* $\dot{V}O_{2max}$ *in l/min* (C). P = *0.032 for the association of a low ponderal index with the metabolic syndrome in men engaging in <25 min/week strenuous physical activity;* P = *0.036 with a* $\dot{V}O_{2max}$ *(ml · kg^{-1} · min^{-1}) in the lowest 40%; and* P = *0.028 with a* $\dot{V}O_{2max}$ *(l/min) below the median.* P *for the respective associations in active or fit men was 0.43, 0.83, and 0.90, respectively.*

enhanced in less fit men (Table 5). The association of the ponderal index with metabolic syndrome was also absent in more fit men (Fig. 1*B* and *C*). In contrast, the likelihood of having the metabolic syndrome was more than twofold greater in unfit men who had a ponderal index in the lower third at birth. In statistical testing, however, the multiplicative interaction of cardiorespiratory fitness and the ponderal index at birth was not significant ($P = 0.27$ for the interaction between thinness at birth and $\dot{V}O_{2max}$ in ml · kg^{-1} · min^{-1}; $P = 0.31$ for the interaction between thinness at birth and $\dot{V}O_{2max}$ in l/min).

CONCLUSIONS — Nondiabetic middle-aged men who were thin at birth or who had a low birth weight had higher fasting insulin and glucose concentrations and were at least two times more likely to have the metabolic syndrome. Moreover, this association was present also in men without CVD, suggesting that thinness at birth also predisposes the metabolic syndrome in its earlier stages, even before development of diabetes or CVD. Perhaps the most compelling new finding of our study was that regular vigorous LTPA or good cardiorespiratory fitness seemed to attenuate or abolish the association of thinness at birth with insulin resistance and the metabolic syndrome.

From a clinical and public health standpoint, it is important to focus on the metabolic syndrome itself rather than its components, because of the commonness of the metabolic syndrome (20,29) and its association with subsequent development of diabetes and CVD (1,3,20,21). Several studies have suggested an association of small size at birth with the metabolic syndrome itself (9,14,15), but these studies have used widely varying and unvalidated definitions. Using a modified and validated WHO definition (20), we demonstrate that men who had a ponderal index or birth weight in the lower third were at least twofold more likely than men in the upper third to have the metabolic syndrome. Adjustment for childhood or adult socioeconomic status had no effect, and adjustment for current BMI, if anything, strengthened the association.

According to the thrifty phenotype hypothesis, in utero undernourishment results in redistribution of blood flow and changes the production of fetal and placental hormones that control growth and

Table 5—*Age-adjusted association of the ponderal index at birth categorized into thirds with fasting insulin and glucose levels and insulin sensitivity, stratified by cardiorespiratory fitness (ml · kg^{-1} · min^{-1} · 40th percentile)*

Ponderal index (thirds)	VO_{2max} <28.6 ml · kg^{-1} · min^{-1} (n = 164)	VO_{2max} ≥28.6 ml · kg^{-1} · min^{-1} (n = 247)
Fasting serum insulin levels (mU/l)		
<26.31 kg/m^3	15.0 (13.1–16.9)	9.3 (8.3–10.2)
26.31–27.72 kg/m^3	11.8 (9.7–13.8)	9.7 (8.8–10.7)
>27.72 kg/m^3	12.3 (9.9–13.5)	9.0 (8.1–9.9)
P value, lowest versus upper two thirds	0.009	0.86
P for the interaction between fitness and thinness at birth	0.009	
Fasting blood glucose levels (mmol/l)		
<26.31 kg/m^3	4.85 (4.72–4.98) mg/dl, 83.4	4.58 (4.47–4.68) mg/dl, 82.5
26.31–27.72 kg/m^3	4.60 (4.46–4.74) mg/dl, 82.9	4.56 (4.45–4.68) mg/dl, 82.2
>27.72 kg/m^3	4.50 (4.36–4.63) mg/dl, 81.1	4.50 (4.39–4.60) mg/dl, 81.1
P value, lowest versus upper two-thirds	<0.001	0.48
P for the interaction between fitness and thinness at birth	0.020	
Insulin sensitivity index		
<26.31 kg/m^3	0.457 (0.444–0.470)	0.501 (0.488–0.513)
26.31–27.72 kg/m^3	0.475 (0.461–0.488)	0.502 (0.490–0.515)
>27.72 kg/m^3	0.481 (0.468–0.495)	0.510 (0.498–0.522)
P value, lowest versus upper two-thirds	0.014	0.44
P for the interaction between fitness and thinness at birth	0.15	

Data are means (95% CI).

metabolism (2,16). These changes may be reflected as reduced fetal growth and decreased cell mass, especially in muscle, liver, and β-cell islets, and may result in metabolic and endocrine "programming," with permanent changes in, for instance, metabolism and action of insulin and IGFs, cortisol levels, sex hormones, and growth hormone (for a review on the human and experimental evidence, see ref. 17). Thinness at birth is believed to be largely a consequence of the fetal environment, but genetic factors also play a role (18).

The association of thinness at birth with hyperinsulinemia and the metabolic syndrome seemed to be enhanced in sedentary men but absent in men engaging in at least 25 min/week of strenuous lifestyle and sporting physical activity. The study may be underpowered, especially for showing a statistically significant multiplicative interaction. These findings are nonetheless strongly suggestive of a relevant biological interaction and imply that thinness at birth is a modifiable risk factor for hyperinsulinemia and the metabolic syndrome. In intervention studies, physical exercise has, to variable degrees and at least in the short term, decreased weight and visceral fat accumulation (30,31), increased HDL cholesterol and decreased triglyceride levels (31), decreased blood pressure (31), and improved insulin sensitivity (30). For most metabolic and disease end points, vigorous physical activity seems to provide additional benefits beyond low- and moderate-intensity exercise (31). We have recently extended these findings, showing that middle-aged men engaging in at least 1 h of vigorous leisure-time activity weekly were nearly three times less likely to develop the metabolic syndrome during follow-up than sedentary men (6). In that same study, men with a high VO_{2max} were also much less likely to develop the metabolic syndrome, even after adjustment for age and BMI.

Cardiorespiratory fitness also seemed to modify the association of thinness at birth with hyperinsulinemia, elevated fasting glucose levels, and the metabolic syndrome in middle age. Again, the association was enhanced in unfit men but absent in fit men. The statistical interaction of thinness at birth with hyperinsulinemia and elevated fasting glucose levels was clear. Despite the striking appearance otherwise in Fig. 1*B* and *C*, the multiplicative interaction was not statistically significant. These overall findings are again strongly suggestive of a potentially important biological interaction. Cardiorespiratory fitness has been used as a proxy for or as an objective measure of LTPA. Indeed, vigorous LTPA and VO_{2max} are quite strongly correlated (r = 0.40) in the KIHD cohort (6) despite the inherent problems in quantifying physical activity. A strong genetic component is nonetheless present (32). Furthermore, especially cardiorespiratory fitness is closely related to the metabolic syndrome (33). It seems clear, however, that the modifying effect of vigorous physical activity and cardiorespiratory fitness is not due to confounding with thinness at birth, because thinness at birth was not related to either the duration of vigorous LTPA or VO_{2max} during middle age.

Our study has several important limitations. Records on birth size were available for only part of the KIHD cohort.

After adjusting for age, however, there was no difference in the main clinical and biochemical measures between men with and without birth records. Information on gestational age was not available. Nonetheless, in previous studies adjustment for gestational age has not attenuated the association of small size at birth with insulin resistance, glucose intolerance, diabetes, or CVD (8,13,34,35). Study size limited more detailed assessment of the modifying role of physical activity and fitness. Noteworthy strengths include a population-based design, detailed assessment of lifestyle and sporting LTPA with a validated questionnaire (26,27), direct measurement of $V_{O_{2max}}$ during a maximal exercise test, assessment of childhood socioeconomic status, and use of an accepted and validated definition of the metabolic syndrome.

Small size at birth was associated with the metabolic syndrome in middle-aged men already in the early stages of the syndrome, before development of diabetes or CVD. Vigorous LTPA and cardiorespiratory fitness seemed to modify the association of thinness at birth with the metabolic syndrome such that the association was absent in active or more fit men but enhanced in sedentary and unfit men. These findings support previous studies showing that thinness at birth may carry with it lifelong metabolic consequences, but suggest that regular strenuous physical activity and maintenance of cardiorespiratory fitness may alleviate or eliminate those consequences.

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References

1. Reaven GM: Banting Lecture 1988: role of insulin resistance in human disease. *Diabetes* 37:1595–1607, 1988
2. Phillips DI: Insulin resistance as a programmed response to fetal undernutrition. *Diabetologia* 39:1119–1122, 1996
3. Liese AD, Mayer-Davis EJ, Haffner SM: Development of the multiple metabolic syndrome: an epidemiologic perspective. *Epidemiol Rev* 20:157–172, 1998
4. Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 344:1343–1350, 2001
5. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393–403, 2002
6. Laaksonen DE, Lakka HM, Salonen JT, Niskanen LK, Rauramaa R, Lakka TA: Low levels of leisure-time physical activity and cardiorespiratory fitness predict development of the metabolic syndrome. *Diabetes Care* 25:1612–1618, 2002
7. Barker DJ, Osmond C, Golding J, Kuh D, Wadsworth ME: Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. *BMJ* 298:564–567, 1989
8. Phillips DI, Barker DJ, Hales CN, Hirst S, Osmond C: Thinness at birth and insulin resistance in adult life. *Diabetologia* 37:150–154, 1994
9. Valdez R, Athens MA, Thompson GH, Bradshaw BS, Stern MP: Birthweight and adult health outcomes in a biethnic population in the USA. *Diabetologia* 37:624–631, 1994
10. 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
11. Mi J, Law C, Zhang KL, Osmond C, Stein C, Barker D: Effects of infant birthweight and maternal body mass index in pregnancy on components of the insulin resistance syndrome in China. *Ann Intern Med* 132:253–260, 2000
12. Eriksson JG, Forsen T, Tuomilehto J, Jaddoe VW, Osmond C, Barker DJ: Effects of size at birth and childhood growth on the insulin resistance syndrome in elderly individuals. *Diabetologia* 45:342–348, 2002
13. Innes KE, Byers TE, Marshall JA, Baron A, Orleans M, Hamman RF: Association of a woman's own birth weight with subsequent risk for gestational diabetes. *JAMA* 287:2534–2541, 2002
14. Barker DJ, Hales CN, Fall CH, Osmond C, Phipps K, Clark PM: Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. *Diabetologia* 36:62–67, 1993
15. Byberg L, McKeigue PM, Zethelius B, Lithell HO: Birth weight and the insulin resistance syndrome: association of low birth weight with truncal obesity and raised plasminogen activator inhibitor-1 but not with abdominal obesity or plasma lipid disturbances. *Diabetologia* 43:54–60, 2000
16. Barker DJ, Gluckman PD, Godfrey KM, Harding JE, Owens JA, Robinson JS: Fetal nutrition and cardiovascular disease in adult life. *Lancet* 341:938–941, 1993
17. Holness MJ, Langdown ML, Sugden MC: Early-life programming of susceptibility to dysregulation of glucose metabolism and the development of type 2 diabetes mellitus. *Biochem J* 349:657–665, 2000
18. Eriksson JG, Lindi V, Uusitupa M, Forsen TJ, Laakso M, Osmond C, Barker DJ: The effects of the Pro12Ala polymorphism of the peroxisome proliferator-activated receptor-γ2 gene on insulin sensitivity and insulin metabolism interact with size at birth. *Diabetes* 51:2321–2324, 2002
19. World Health Organization: *Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Part 1: Diagnosis and Classification of Diabetes Mellitus: Provisional Report of a WHO Consultation*. Geneva, World Health Org., 1999
20. Laaksonen DE, Lakka HM, Niskanen LK, Kaplan GA, Salonen JT, Lakka TA: Metabolic syndrome and development of diabetes mellitus: application and validation of recently suggested definitions of the metabolic syndrome in a perspective cohort study. *Am J Epidemol* 156:1070–1077, 2002
21. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, Salonen JT: The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 288:2709–2716, 2002
22. Salonen JT: Is there a continuing need for longitudinal epidemiologic research? The Kuopio Ischaemic Heart Disease Risk Factor Study. *Ann Clin Res* 20:46–50, 1988
23. Balkau B, Charles MA: Comment on the provisional report from the WHO consultation: European Group for the Study of Insulin Resistance (EGIR). *Diabet Med* 16: 442–443, 1999
24. Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, Sullivan G, Quon MJ: Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. *J Clin Endocrinol Metab* 85:2402–2410, 2000
25. Lynch JW, Kaplan GA, Cohen RD, Kauhanen J, Wilson TW, Smith NL, Salonen JT: Childhood and adult socioeconomic status as predictors of mortality in Fin-

land. *Lancet* 343:524–527, 1994
26. Lakka TA, Salonen JT: Intra-person variability of various physical activity assessments in the Kuopio Ischaemic Heart Disease Risk Factor Study. *Int J Epidemiol* 21:467–472, 1992
27. Lakka TA, Venäläinen JM, Rauramaa R, Salonen R, Tuomilehto J, Salonen JT: Relation of leisure-time physical activity and cardiorespiratory fitness to the risk of acute myocardial infarction. *N Engl J Med* 330:1549–1554, 1994
28. Salonen JT, Nyyssönen K, Korpela H, Tuomilehto J, Seppänen R, Salonen R: High stored iron levels are associated with excess risk of myocardial infarction in eastern Finnish men. *Circulation* 86:803–811, 1992
29. Ford ES, Giles WH, Dietz WH: Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA* 287:356–359, 2002
30. Ross R, Dagnone D, Jones PJ, Smith H, Paddags A, Hudson R, Janssen I: Reduction in obesity and related comorbid conditions after diet-induced weight loss or exercise-induced weight loss in men: a randomized, controlled trial. *Ann Intern Med* 133:92–103, 2000
31. U.S. Department of Health and Human Services: *Physical Activity and Health: A Report of the Surgeon General*. Atlanta, GA, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, 1996
32. Bouchard C: Genetics and the metabolic syndrome. *Int J Obes Relat Metab Disord* 19 (Suppl. 1):S52–S59, 1995
33. Whaley MH, Kampert JB, Kohl HW 3rd, Blair SN: Physical fitness and clustering of risk factors associated with the metabolic syndrome. *Med Sci Sports Exerc* 31:287–293, 1999
34. Phipps K, Barker DJ, Hales CN, Fall CH, Osmond C, Clark PM: Fetal growth and impaired glucose tolerance in men and women. *Diabetologia* 36:225–228, 1993
35. Leon DA, Lithell HO, Vagero D, Koupilova I, Mohsen R, Berglund L, Lithell UB, McKeigue PM: Reduced fetal growth rate and increased risk of death from ischaemic heart disease: cohort study of 15 000 Swedish men and women born 1915–29. *BMJ* 317:241–245, 1998