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Original Article

The role of fitness in the association between fatness and cardiometabolic risk from childhood to adolescence

Brouwer SI, Stolk RP, Liem ET, Lemmink KAPM, Corpeleijn E. The role of fitness in the association between fatness and cardiometabolic risk from childhood to adolescence. *Pediatric Diabetes* 2013; 14: 57–65.

Background: Fatness and fitness both influence cardiometabolic risk.

Objective: The purpose of this study was to investigate whether childhood fatness and increasing fatness from childhood to adolescence are associated with cardiometabolic risk during adolescence and how fitness affects this association.

Subjects and methods: Of 565 adolescents (283 boys and 282 girls) from the TRacking Adolescents Individual Life Survey (TRAILS) data on anthropometric parameters (age 11 and 16), metabolic parameters, and fitness (age 16) were available. Body mass index and skinfolds were used as measures for fatness. Increasing fatness was calculated by subtracting Z-scores for fatness at age 11 from Z-score fatness at age 16. Cardiometabolic risk was calculated as the average of the standardized means of mean arterial pressure, fasting serum triglycerides, high-density lipoprotein-cholesterol, glucose, and waist circumference. Insulin resistance was calculated by homeostasis model assessment-insulin resistance (HOMA-IR). Fitness was estimated as maximal oxygen consumption (VO₂max) during a shuttle run test.

Results: Boys showed a higher clustered cardiometabolic risk when compared to girls ($p < 0.01$). Childhood fatness (age 11) and increasing fatness were independently associated with cardiometabolic risk during adolescence. In boys, high fitness was related to a reduced effect of increasing fatness on clustered cardiometabolic risk. Childhood fatness, increasing fatness, and fitness were independently associated with HOMA-IR. Moreover, in boys this association was dependent of fatness.

Conclusions: Childhood fatness and increasing fatness are associated with increased cardiometabolic risk and HOMA-IR during adolescence, but a good fitness attenuates this association especially in fat boys.

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Key words: body mass index – insulin resistance – metabolic syndrome – physical fitness – skinfold thickness

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According to the World Health Organization, 4.9–22.5% of European boys are overweight and 2.4–0.3% are obese. In girls, overweight ranges from 6.9 to 19.9% and obesity from 2.0 to 12.3% (1). In children, overweight is of clinical interest because of its association with metabolic risk factors for cardiovascular disease, such as hyperlipidemia,

hypertension (2, 3), hyperglycemia, and insulin resistance (4). Studies on tracking overweight report an increased risk of overweight and obese youth becoming overweight adults (5) and therefore childhood overweight has significant long-term consequences (6).

Several studies have shown that, in adults, higher cardio respiratory fitness attenuates cardiometabolic

risk (7, 8). Especially among those with obesity, fitness attenuates cardiometabolic risk. This finding generated the 'fat but fit' paradigm which states that fat but fit people have healthier cardiometabolic outcomes than fat but unfit people, and are sometimes even as healthy as unfit but not fat people. Cross-sectional studies on children and adolescents have also reported that among children and adolescents with high fatness, high fitness is related to decreased cardiometabolic risk (9).

The influence of childhood fatness, and in particular the changes in fatness on cardiometabolic risk and how fitness effects this association has not been studied in depth. Therefore, the aim of this study was to investigate whether childhood fatness and increasing fatness from childhood to adolescence are associated with cardiometabolic risk during adolescence and how fitness affects this association.

Methods

Subjects

Data was collected as part of the 'TRacking Adolescents' Individual Lives Survey' (TRAILS) (10). TRAILS is a prospective cohort study in healthy Dutch children who have been followed from age 11 into adolescence. TRAILS participants were selected from five municipalities in the North of The Netherlands. This study involves data from the first (mean age 11.4 yr, SD=0.56) and third (mean age 16.1 yr, SD=0.5) examination which ran from March 2001 to July 2002 and from September 2005 to December 2007, respectively. The initial TRAILS population consisted a total of 2230 children. Biochemical data and fitness were only measured in the third examination. For financial and practical reasons, schools were selected at random to participate in the collection of biochemical measures and/or fitness test. For this study 1665 children were excluded because no data were available on biochemical measures or fitness measures or children suffered from physical complaints which interfered with measurement of fitness (knee injuries). The final sample size included 565 children (283 boys and 282 girls). The study protocol was approved by the National Dutch Medical Ethics Committee on research involving human subjects. Written informed consent was obtained from the children and the children's parents or custodians.

Measures of fatness and associated metabolic factors

Height, weight, waist circumference, and skinfolds were measured at school after removing shoes and heavy clothing. Weight was measured in kilograms

using a calibrated analogue Seca balance scale (Model 770; SECA Corp., Hamburg, Germany). Height was measured in centimeters using a Seca stadiometer (model 214; SECA Corp.). Waist circumference was measured in centimeters taken midway between the lowest rib and the iliac crest. Four skinfolds (triceps, biceps, subscapular, and suprailiac) were measured by trained study personnel using standardized protocols and calibrated equipment, i.e., a Harpenden skinfold caliper (CMS instruments, London, UK). Glucose, insulin, triglycerides, total cholesterol, high- and low-density lipoprotein-cholesterol (HDL-C) were determined from a fasting blood sample according to standard laboratory procedures. Low-density lipoprotein-cholesterol was calculated according to Friedwald's equation (11). Insulin resistance was calculated as homeostasis model assessment-insulin resistance (HOMA-IR) using the following equation: $[(\text{insulin}) \times (\text{glucose})] / 22.5$ (12).

Resting diastolic blood pressure (DBP) and systolic blood pressure (SBP) were measured using Dinamap Critikon® 1846SX (Critikon® inc., Tampa, FL, USA) on the right arm in a horizontal resting position. Mean arterial pressure (MAP) was calculated as: $\text{DBP} + [1/3 \times (\text{SBP} - \text{DBP})]$.

Clustered cardiometabolic risk score

A continuous variable was calculated for the clustered cardiometabolic risk. Waist circumference, fasting glucose, triglycerides, MAP, and HDL-C were transformed into Z-score and added. The metabolic risk score was calculated as the sum for the five Z-scores divided by 5. Thereby triglycerides were Ln-transformed to obtain a normal distribution and HDL-C was inverted. In the same manner a clustered metabolic Z-score was obtained with the exclusion of waist circumference.

Cardio respiratory fitness

A 20-m shuttle run test was used as an objective and validated measurement to assess fitness (13). Participants had to run back and forth on a 20-m course and pivot on the 20-m line, while keeping pace with audio signals emitted from a pre-recorded compact disc. The initial speed was 8 km/h and the speed increased by 0.5 km/h every minute. In a subsample of 272 (48.1%) participants, heart rate (HR) monitoring was performed using Polar Team System series 1 (Polar, Kempele, Finland). In this group, an extra criterion for maximum exertion was applied as a HR above 185 beats/min. Performance on the test, measured by $\text{VO}_{2\text{max}}$, did not differ between participants wearing a HR monitor and participants who did

not (46.3 ± 7.4 mL/min/kg, 46.3 ± 6.8 mL/min/kg; $p = 0.212$, respectively). The estimated VO_2max was calculated using the following equation: $\text{VO}_2\text{max} = 31.025 + (3.238 \times \text{speed}) - (3.248 \times \text{age}) + 0.1536 \times (\text{speed} \times \text{age})$ (14).

Pubertal stage

The stage of pubertal development at age 11 yr was assessed by parent ratings using schematic drawings of secondary sex characteristics associated with the five Tanner stages (15, 16). At age 16 yr, the Pubertal Development Scale (PDS) questionnaire (17) was used to assess pubertal development filled in by the adolescents themselves. The PDS questionnaire was recorded into five stages comparable to the Tanner stages (18).

Statistics

Data were analyzed using SPSS 18.0. Boys and girls were analyzed separately due to complex interactions between pubertal stage, fatness, CRF, and cardiometabolic risk that were related to gender differences. Triglycerides, insulin, and HOMA-IR were Ln-transformed because of lack of normality. A two-tailed Student's *t*-test was used to test for gender differences or Fisher's exact test in case of categorical data. Increasing fatness was calculated by subtracting Z-scores for fatness [body mass index (BMI) and skinfolds] at age 11 from Z-score fatness at age 16. The associations between childhood fatness, increasing fatness and fitness, and cardiometabolic outcomes during adolescence were studied by Pearson correlations. Regression analysis was performed to identify the independent contribution of fatness, increasing fatness and fitness to the clustered cardiometabolic risk score, and HOMA-IR. Children were categorized into four groups based on the increasing fatness. Two groups were created for children with negative scores (ΔBMI 1 < -1 and ΔBMI 2 between -1 and 0), which means that those children gained the least weight; two groups were created for children with positive scores (ΔBMI 4 > 1 and ΔBMI 3 between 0 and 1), which means that those children gained the most weight. In model 1, we evaluated the association between childhood fatness (age 11) and the clustered cardiometabolic risk score in adolescence, adjusted for age and study location, Tanner stage (age 11), and pubertal development stage (age 16). In model 2, increasing fatness was added to test its relation with the clustered cardiometabolic risk score. In model 3, fitness was added to evaluate its contribution independent of fatness and increasing fatness. In the final model, model 4, an interaction between fitness and increasing fatness was added.

Missing data were replaced with the series mean if missings were less than 1%. Missing data for skinfolds at age 11 (6.4% for triceps, subscapular, and suprailiacal; 23% for biceps) were replaced by imputation using available relevant variables (gender, age, weight at age 11 and age 16, height age 11 and age 16, and other skinfolds at age 16). Missing data for PDS (9.6%) were replaced by multiple imputation using available relevant variables [gender, age, and Tanner stage (age 11)] and anthropometric and biochemical measures.

Results

Gender differences

In boys, 11.8% were overweight at age 11 and 10.6% of the boys were overweight at age 16. In girls, 10.6% were overweight at age 11 and 10% of the girls were overweight at age 16 according to the international accepted definition (19). Table 1 shows that at the age of 11 boys and girls did not differ regarding BMI, whereas the sum of skinfolds was higher in girls compared to boys ($p = 0.02$). At age 16, girls had higher BMI ($p = 0.04$) and sum of skinfolds ($p < 0.01$) compared to boys, whereas boys showed higher clustered cardiometabolic risk score when compared to girls ($p < 0.01$). This was due to higher MAP ($p = 0.01$), triglycerides ($p = 0.02$), fasting glucose ($p < 0.01$), and lower HLD-C ($p < 0.01$). As expected, boys had higher fitness ($p < 0.01$) compared to girls.

Childhood fatness, increasing fatness, VO_2max , and cardiometabolic risk

Table 2 shows that childhood fatness in boys correlated to the clustered cardiometabolic risk with and without waist at age 16. Childhood fatness in girls was related to the clustered cardiometabolic risk at age 16, however, this was fully explained by a correlation with waist circumference. Increasing fatness was significantly correlated to the clustered cardiometabolic risk in both boys and in girls and several, but not all, individual cardiometabolic risk factors at age 16. In boys and girls, VO_2max correlated inversely with the clustered cardiometabolic risk, however, in girls this correlation was mainly explained by a correlation with waist circumference. Regression was used to study the associations between childhood fatness, increasing fatness, fitness, and the interaction between increasing fatness and fitness to the clustered cardiometabolic risk with adjustments for age, study location, and pubertal stage. Data are presented in Table 3. Only models using BMI as a measure for fatness are presented, because BMI showed stronger associations with metabolic outcomes compared to skinfolds. In boys as well

Table 1. Descriptive characteristics of Dutch adolescents in the TRAILS cohort

	Boys (N = 283)	Girls (N = 282)	p-Value
Age 11			
Age	11.1 ± 0.5	11.0 ± 0.6	0.06
BMI (kg/m ²)	17.6 ± 2.4	17.6 ± 2.4	0.92
Sum of skinfolds (cm)	38.8 ± 18.8	43.8 ± 18.3	0.02
Pubertal stage (%)	31.1, 65.0, 3.9, 0, 0	35.8, 41.5, 17.4, 5.0, 0.4	<0.01
Age 16			
Age	16.1 ± 0.5	16.0 ± 0.5	0.25
BMI (kg/m ²)	20.7 ± 2.7	21.1 ± 2.5	0.04
Sum of skinfolds (cm)	38.3 ± 19.6	57.1 ± 17.0	<0.01
Pubertal stage (%)	0.7, 1.4, 33.2, 64.7, 0	0, 0, 3.5, 75.9, 20.6	<0.01
Waist circumference (cm)	74.4 ± 7.3	74.0 ± 6.5	0.37
DBP (mmHg)	59.7 ± 6.4	61.5 ± 6.9	0.01
SBP (mmHg)	121.4 ± 12.0	113.4 ± 10.2	<0.01
MAP (mmHg)	80.2 ± 6.9	78.8 ± 7.1	0.01
LDL-C (mmol/L)	2.16 ± 0.61	2.33 ± 0.61	0.01
HDL-C (mmol/L)	1.40 ± 0.29	1.54 ± 0.31	<0.01
Total-C (mmol/L)	3.62 ± 0.67	3.93 ± 0.68	<0.01
Triglycerides (mmol/L)	0.70 (0.53, 0.87)	0.61 (0.48, 0.88)	0.02
Glucose (mmol/L)	4.60 ± 0.42	4.48 ± 0.46	<0.01
Insulin (mU/L)	11.8 (8.6, 15.0)	12.25 (9.6, 16.0)	0.03
HOMA-IR	2.35 (1.66, 3.07)	2.48 (1.90, 3.15)	0.19
Clustered cardiometabolic risk	0.08 ± 0.57	−0.08 ± 0.50	<0.01
Clustered cardiometabolic risk without waist	0.09 ± 0.59	−0.09 ± 0.54	<0.01
VO ₂ max (mL/min/kg)	50.3 ± 6.4	42.3.0 ± 5.2	<0.01

BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein-cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; LDL-C, low-density lipoprotein-cholesterol; MAP, mean arterial pressure; SBP, systolic blood pressure; TRAILS, TRacking Adolescents Individual Life Survey.

Data are presented as means ± SD. Ln-transformed data are presented as median (25th–75th percentile). Tanner stage and pubertal stage are presented as % in phase 1–5 (prepubertal, early pubertal, mid-pubertal, late pubertal, and postpubertal, respectively). Clustered cardiometabolic risk is presented as a Z-score with average = 0 and SD = 1. A two-tailed Student's *t*-test for independent samples was used to test for gender differences. Differences in categorical data were tested with the Fisher's exact test.

as in girls, childhood fatness predicted clustered cardiometabolic risk during adolescence (model 1). Model 2 showed that independently from childhood fatness, increasing fatness between age 11 and 16 was associated with clustered cardiometabolic risk. Weight gain in Δ BMI 1, Δ BMI 2, Δ BMI 3, and Δ BMI 4 was 13.6 ± 7.5 , 19.6 ± 5.3 , 26.0 ± 5.5 , and 31.4 ± 7.2 kg, respectively. Model 3 shows that in boys, fitness was associated with clustered cardiometabolic risk independent of fatness and increasing fatness. In girls, there was only a trend for this association. The interaction between increasing fatness and fitness (model 4) was only significant in boys. When adding the interaction to the model, the independent effect of fitness disappeared ($\beta = 0.023$; 95% CI: -0.006 , 0.053), whereas the influence of increasing fatness increased. This interaction in boys was only significant when using BMI as a measure for fatness and not when skinfolds were used as a measure for fatness ($\beta = -0.008$; 95% CI: -0.08 , 0.003). After excluding waist from the clustered cardiometabolic risk the interaction was no longer significant ($\beta = 0.000$; 95% CI: -0.014 , 0.012). This interaction between fatness and fitness is graphically depicted in Fig. 1A, B.

Childhood fatness, increasing fatness, VO₂max, and HOMA-IR

In boys, childhood fatness was related to insulin and HOMA-IR at age 16, whereas in girls increasing fatness was positively related to HOMA-IR (Table 2). VO₂max also correlated inversely with insulin and HOMA-IR. These correlations were moderate for boys ($r = -0.314$, -0.310 , respectively) and small to moderate for girls ($r = -0.180$, -0.186 , respectively). When adjusting for age, study location, and pubertal development, childhood fatness predicted HOMA-IR in boys (model 1) but not in girls. Increasing fatness (model 2) was associated with HOMA-IR independent of fatness (age 11) in girls but not in boys. Fitness (model 3) was associated with HOMA-IR independent of fatness and increasing fatness in both boys and girls. Only in boys was there a significant interaction between increasing fatness and fitness (model 4). As in the clustered cardiometabolic risk, when adding the interaction to the model, the independent effect of fitness disappeared ($\beta = 0.008$; 95% CI: -0.22 , 0.038). Furthermore, the effect of increasing fatness increased and became significant ($\beta = 0.592$; 95% CI: 0.056 , 1.129). Thus for

Table 2. Correlations between BMI age 11, skinfolds age 11, increasing fatness, VO₂max, and the metabolic risk factors at age 16

Outcome measures (age 16)	BMI (age 11)		Skinfolds (age 11)		Δ BMI (increasing fatness at age 11 to 16)*		Δ Skinfolds (increasing fatness at age 11 to 16)*		VO ₂ max (age 16)	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
Clustered cardiometabolic risk	0.476**	0.163**	0.466**	0.177**	0.193**	0.317**	0.205**	0.172**	−0.253**	−0.174**
Clustered cardiometabolic risk (without waist)	0.308**	−0.017	0.297**	0.025	0.094	0.219**	0.122*	0.094	−0.175**	−0.103
Waist circumference (cm)†	0.590**	0.471**	0.536**	0.414**	0.308**	0.343**	0.278**	0.245**	−0.289**	−0.229**
MAP (mmHg)†	0.171**	0.021	0.188**	−0.034	0.117*	0.009	0.096	0.049	−0.120*	0.065
DBP (mmHg)	0.026	−0.024	0.079	−0.050	0.067	0.004	0.060	0.062	−0.156**	0.071
SBP (mmHg)	0.292**	0.053	0.269**	−0.080	0.157**	0.126*	0.138*	0.134*	−0.026	0.061
Triglycerides (mmol/L)†	0.259**	−0.073	0.247**	−0.042	0.113	0.137*	0.173**	0.048	−0.119*	−0.086
HDL-C (mmol/L)†	−0.219**	−0.015	−0.103	−0.057	0.068	−0.189**	0.031	−0.072	0.007	0.159**
LDL-C (mmol/L)	0.171	0.015	0.218**	−0.041	0.149*	0.078	0.168**	0.082	−0.107	0.045
Total-C (mmol/L)	0.150*	0.020	0.217**	−0.047	0.154**	−0.010	0.162**	0.049	−0.086	0.089
Glucose (mmol/L)†	0.073	−0.006	0.155**	0.067	0.048	0.135*	0.035	0.031	−0.166**	−0.042
Insulin (mU/L)	0.207**	0.042	0.300**	0.026	0.052	0.161**	0.083	0.195**	−0.310**	−0.186**
HOMA-IR	0.204**	0.037	0.304**	0.039	0.056	0.180**	0.082	0.188**	−0.314**	−0.180**

BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein-cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; LDL-C, low-density lipoprotein-cholesterol; MAP, mean arterial pressure; SBP, systolic blood pressure.

Data are Pearson correlation coefficients; * $p < 0.05$; ** $p < 0.01$; Δ BMI: Z-score BMI age 16 to Z-score BMI age 11.

*Increasing fatness was calculated by subtracting Z-scores for fatness (BMI and skinfolds) at age 11 from Z-score fatness at age 16.

† Factors of the clustered cardio metabolic risk.

boys the contribution of fitness to HOMA-IR depends on the growth in BMI between age 11 and 16. The larger this growth the higher the contribution of fitness. This interaction between fatness and fitness is graphically depicted in Fig. 2A, B.

Discussion

This study shows that childhood fatness and increasing fatness are independently associated with increased cardiometabolic risk and HOMA-IR during adolescence, and that good fitness attenuates this association especially in fat boys. In addition, in boys the effect of fitness on cardiometabolic risk and HOMA-IR depends on the increasing fatness. In girls, fitness only influenced HOMA-IR but not the cardiometabolic risk independent of childhood fatness and increasing fatness.

In boys, measures of childhood fatness correlated to the clustered cardiometabolic risk either with or without waist circumference during adolescence. In girls, measures of childhood fatness were also correlated with the clustered cardiometabolic risk; however, this was fully explained by a correlation with waist circumference. Associations between childhood

fatness and individual cardiometabolic risk factors in later life were found before in a study of 31 obese children who were followed from the age of 13 till age 22 (20). Another study showed that the degree of fatness in childhood is tightly linked to adverse cardiometabolic outcomes in adulthood (21). An interesting question that rises is whether there is an association between the initial degree of childhood fatness and later cardiometabolic risk or that childhood fatness is only relevant if it has tracked into later life. This study shows that, independent of the effects of childhood fatness, increasing fatness from childhood into adolescence is associated with clustered cardiometabolic risk and HOMA-IR during adolescence. A study with 186 obese adolescents who were followed for 19 months found that fatness was linked to individual cardiometabolic risk factors and changes in insulin sensitivity (22). Cardiometabolic risk factors and changes in insulin sensitivity were assessed at baseline and after 19 ± 7 months. The cohort was stratified into three categories based on the 25th and 75th percentile of BMI Z-score change. Subjects who reduced their BMI Z-score significantly decreased their fasting and 2-h glucose levels and triglyceride levels and increased their high density lipoprotein cholesterol

Table 3. (a) Association between BMI, Δ BMI, VO_2 max, Δ BMI $\times$ VO_2 max, and clustered cardiometabolic risk and (b) between BMI, Δ BMI, VO_2 max, Δ BMI $\times$ VO_2 max, and HOMA-IR

	Boys (N = 283)			Girls (N = 282)		
	Beta coefficient (95% CI)	aR ²	R ² change	Beta coefficient (95% CI)	aR ²	R ² change
(a) Association between BMI, Δ BMI, VO_2 max, Δ BMI $\times$ VO_2 max, and clustered cardiometabolic risk						
Model 1	BMI (age 11)	0.107** (0.082, 0.132)	0.221	0.035* (0.010, 0.059)	0.106	0.017
Model 2	BMI (age 11)	0.130** (0.106, 0.155)	0.317	0.055** (0.032, 0.079)	0.215	0.119
	Δ BMI	0.263** (0.181, 0.345)		0.233** (0.160, 0.306)		
Model 3	BMI (age 11)	0.121** (0.096, 0.145)	0.338	0.051** (0.027, 0.075)	0.221	0.006
	Δ BMI	0.255** (0.175, 0.336)		0.225** (0.152, 0.299)		
	VO_2 max	-0.014* (-0.023, -0.005)		-0.009 (-0.019, 0.001)		
Model 4	BMI (age 11)	0.117** (0.092, 0.141)	0.351	0.051** (0.027, 0.075)	0.219	0
	Δ BMI	0.948** (0.418, 1.477)		0.171** (-0.331, 0.673)		
	VO_2 max	0.023 (-0.006, 0.053)		-0.013 (-0.046, 0.021)		
	Δ BMI $\times$ VO_2 max	-0.015* (-0.026, -0.004)		0.001 (-0.011, 0.014)		
(b) Association between BMI, Δ BMI, VO_2 max, Δ BMI $\times$ VO_2 max, and HOMA-IR						
Model 1	BMI (age 11)	0.041** (0.017, 0.065)	0.077	0.008 (-0.015, 0.031)	0.084	0
Model 2	BMI (age 11)	0.047** (0.022, 0.072)	0.083	0.017 (-0.007, 0.041)	0.104	0.02
	Δ BMI	0.070 (-0.014, 0.154)		0.101* (0.028, 0.175)		
Model 3	BMI (age 11)	0.033** (0.008, 0.058)	0.144	0.012 (-0.012, 0.036)	0.118	0.014
	Δ BMI	0.059* (-0.022, 0.141)		0.092** (0.018, 0.165)		
	VO_2 max	-0.021** (-0.030, -0.012)		-0.012* (-0.021, -0.002)		
Model 4	BMI (age 11)	0.030* (0.005, 0.055)	0.153	0.013 (-0.011, 0.037)	0.118	0
	Δ BMI	0.592* (0.056, 1.129)		-0.159 (-0.660, 0.343)		
	VO_2 max	0.008 (-0.22, 0.038)		-0.028 (-0.062, 0.006)		
	Δ BMI $\times$ VO_2 max	-0.011* (-0.023, 0.000)		0.006 (-0.006, 0.019)		

aR², adjusted R-square; BMI, body mass index; CI, confidence interval.Model 1: + BMI age 11; Model 2: + Δ BMI; Model 3: + VO_2 max; Model 4: + Δ BMI $\times$ VO_2 max. All models were adjusted for age, study location, Tanner (age 11), and Pubertal Development Scale (age 16). Δ BMI: categorized differences in Z-score BMI age 11 and Z-score BMI age 16; Two groups were created for children with negative scores (< -1 and between -1 and 0), two groups were created for children with positive scores (> 1 and between 0 and 1); Beta coefficients are unstandardized: *p < 0.05; **p < 0.01.

Fig. 1. Interaction between increasing fatness and fitness on cardiometabolic risk in (A) boys and (B) girls. Regression lines are presented for group 1 with lowest up to group 4 with highest increase in body mass index Z-score. Regression coefficients as presented in Table 3a were used for the regression line. Study location, Tanner, and Pubertal Development Scale were kept constant.

Fig. 2. Interaction between increasing fatness and fitness on homeostasis model assessment-insulin resistance in (A) boys and (B) girls. Regression lines are presented for group 1 with lowest up to group 4 with highest increase in body mass index Z-score. Regression coefficients as presented in Table 3b were used for the regression line. Study location, Tanner, and Pubertal Development Scale were kept constant.

in comparison to subjects who increased their BMI Z-score. BMI Z-score changes negatively correlated with changes in insulin sensitivity ($r = -0.36$, $p < 0.001$). Of 67 who had metabolic syndrome at baseline, 33 (50%), most of whom decreased their BMI Z-score, lost the diagnosis. However, these studies used clinical (obese) populations. TRAILS uses a general and not a clinical population. Therefore, the finding of this study can be best compared with the findings of an Australian cohort study in which 172 children were followed from the age of 8 to 15 yr (23). They reported that children who were overweight or obese at 8 yr of age were seven times as likely to have cardiometabolic risk clustering in adolescence than were their peers who were not overweight or obese. They also reported that those with an increased waist circumference at age 8 yr were four times more likely to have cardiometabolic risk clustering in adolescence than were children with a smaller waist circumference. It was concluded that association between measures

of fatness in mid-childhood and later adverse cardiometabolic risk is a result of the tracking of fatness status.

In line with other studies fitness was inversely related to the clustered cardiometabolic risk with or without waist circumference (24, 25) and HOMA-IR (26). In boys, fitness was associated with clustered cardiometabolic risk and HOMA-IR independent of childhood fatness and increasing fatness. In girls, there was only an independent association with HOMA-IR but not with clustered cardiometabolic risk. This could be because of a lack of power or because of the absence of more overweight or obese girls in the study population. Nevertheless, these findings are in line with cross-sectional studies (27) which studied the mediation of fitness on the association between fatness and cardiometabolic risk by stratification. Children and adolescents with ‘high fatness and high fitness’ have better cardiometabolic risk profiles than those classified as ‘high fatness but low fitness’. However,

in these studies it is difficult to determine whether fitness modifies the association between fatness and cardiometabolic risk since fitness and fatness are heavily intertwined. Stratification by fatness does not always solve this problem because groups are not always equally balanced, resulting in lower average BMI in groups with 'fat but fit' children when compared to 'fat and unfit' children.

This study further shows that in boys there is a significant interaction between fitness and fatness which states that high fitness attenuates the association between fatness and clustered cardiometabolic risk especially in those who had higher increases in BMI between age 11 and age 16. For HOMA-IR, comparable results were found. One prospective study in which the association between fatness, fitness, and cardiometabolic risk was found. The Amsterdam Growth and Health Longitudinal Study followed 364 individuals (189 women) from adolescence (age 13) into adulthood (age 36) on fatness, fitness, and cardiometabolic risk (28). This study found independent influences of fatness and fitness on cardiometabolic risk. The associations between fitness and the metabolic syndrome decreased considerably when adjusted for fatness, but the associations remained statistically significant. The authors suggest that poor fitness may be associated with cardiometabolic risk partly because of its associations with body fatness (29) and also because of other mechanisms including insulin resistance (30), sub-clinical inflammation (31), or a common genetic background (32), (33) that predisposes to low fitness and increased cardiometabolic risk.

Limitations and advantages

This study shows some limitations while overweight girls were more often excluded due to missing data on fitness which might result in selection bias. In this study puberty was assessed by using two different methods, one filled in by the parents (Tanner) at the first examination and second filled in by the adolescents (PDS) at the third examination. This might result into a less accurate definition of the maturity status, but does not influence the main outcomes. The advantage of this study is that it shows in a longitudinal design that childhood fatness, increasing fatness, and fitness are independently associated with clustered metabolic risk and HOMA-IR. However, only fatness measures were tracked. In this study, BMI as well as skinfolds were used as measures for fatness. Because BMI showed more obvious associations with the clustered cardiometabolic risk and HOMA-IR compared to skinfold, most of the time results from BMI are presented. This study used a valid measure of fitness and a subsample of participants (48%) was checked

for maximal exhaustion rendering the measurements accurate.

To improve cardiometabolic risk in adolescents, interventions need to focus not solely on reducing fatness but also on physical activities that improve fitness.

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