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Effects of the Active Smarter Kids (ASK) physical activity intervention on cardiometabolic risk factors in children: A cluster-randomized controlled trial

Mette Stavnsbo[a,b,*], Eivind Aadland[a], Sigmund A. Anderssen[a,b], Mai Chinapaw[c], Jostein Steene-Johannessen[b], Lars B. Andersen[a], Geir K. Resaland[d]

[a] Western Norway University of Applied Sciences, Department of Sport, Food and Natural Sciences, Sogndal, Norway
[b] Norwegian School of Sport Sciences, Department of Sports Medicine, Oslo, Norway
[c] Amsterdam University Medical Centers, Amsterdam Public Health research institute, Department of Public and Occupational Health, Amsterdam, the Netherlands
[d] Western Norway University of Applied Sciences, Center for Physically Active Learning, Faculty of Education, Arts and Sports, Sogndal, Norway

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ABSTRACT

The onset of cardiometabolic diseases are recognized to occur in childhood. We aimed to investigate the effect of a school-based cluster-randomized controlled trial of physical activity (PA) on single and clustered cardiometabolic risk factors.

We included 1129 fifth-grade children from 57 schools (≥seven children in each class) in Sogn and Fjordane County, Norway, randomized to 28 intervention schools and 29 control schools. The PA intervention was conducted between November 2014 and June 2015. Cardiometabolic risk factors were waist circumference (WC), systolic blood pressure (SBP), total cholesterol (TC):high-density lipoprotein (HDL)-ratio, triglycerides (TG), homeostatic model assessment (HOMA)-score, and cardiorespiratory fitness (CRF). PA was measured by accelerometry.

No significant intervention effects were found for single or clustered cardiometabolic risk factors. However, in children with the less favorable baseline values, beneficial effects were found for SBP ($p = 0.07$ for group * tertile interaction), TC:HDL ratio ($p = 0.03$ for group * tertile interaction) and the clustered cardiometabolic risk score ($p = 0.01$ for group * tertile interaction). Compared to boys, girls had a greater effect of the intervention on WC ($p = 0.03$ for group * sex interaction) and CRF ($p < 0.001$ for group * sex interaction).

The majority of the children had high PA levels, thus limited potential for change, and we found no effects of the PA intervention on cardiometabolic risk in the total sample. However, the intervention had a significantly enhanced effect on fatness and fitness of girls compared to boys. Furthermore, the data suggest that children with the least favorable cardiometabolic risk profile and therefore most in need of change can benefit from school-based PA interventions.

Trial registration number: Clinicaltrials.gov ID no.: NCT02132494.

1. Introduction

While the onset of cardiometabolic diseases are recognized to occur in early childhood (Berenson et al., 1998; Berenson et al., 1992; Strong et al., 1999; WHO, 2008), physical activity (PA) contributes positively to cardiovascular health in addition to endocrine, cellular, skeletal and mental health (Strong et al., 2005). Importantly, children that increase their amount of regular activity in moderate-to-vigorous PA (MVPA) can improve their cardiorespiratory fitness (CRF) over time (Kristensen et al., 2010), which is a powerful marker of general health in children (Ortega et al., 2008). Low CRF in adults is one of the strongest determinants of overall mortality and morbidity from cardiometabolic diseases (Katzmarzyk et al., 2004; Blair et al., 1996). Unfortunately, children's PA levels decrease from early childhood to adolescence

Abbreviations: ASK, Active smarter kids; BMI, Body mass index; Cluster-RCT, Cluster-randomized controlled trial; CRF, Cardiorespiratory fitness; DBP, Diastolic blood pressure; HDL, High-density lipoprotein; HOMA, Homeostatic model assessment; LDL, Low-density lipoprotein; MVPA, Moderate-to-vigorous physical activity; PA, Physical activity; PE, Physical education; SBP, Systolic blood pressure; SED, Sedentary time; TC, Total cholesterol; WC, Waist circumference

* Corresponding author at: Sogn og Fjordane University College, PO Box 133, N-6856 Sogndal, Norway.
E-mail address: Mette.Stavnsbo@hvl.no (M. Stavnsbo).

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(Hallal et al., 2012; Dalene et al., 2018; Farooq et al., 2018), and some studies indicate that patterns of both PA and inactivity track into adulthood (Malina, 2001; Raitakari et al., 1994). Thus, a major focus of public health initiatives has been to promote PA levels among children.

Children spend a substantial amount of time in school during their first two decades of life (Story et al., 2009). Therefore, the World Health Organization, among others (WHO, 2004; Naylor and McKay, 2009), has emphasized increased PA in schools as an ideal environment for public health interventions. School-based PA interventions have many advantages: all children are included, which ensures PA for all in a non-stigmatizing way regardless of gender, age, weight status, fitness level, parent's socioeconomic status, and or attitude towards PA. Furthermore, the school system offers a stable schedule and can provide increased habitual activity from early in life. However, evidence of the impact of PA interventions on cardiometabolic risk factors in school children is equivocal (Sun et al., 2013; Dobbins et al., 2013; Kriemler et al., 2011; Pozuelo-Carrascosa et al., 2017). Notably, the children with the most unfavorable cardiometabolic risk profile might experience the greatest effects (Resaland et al., 2018a), which supports a population approach for reaching high-risk children.

The aim of this paper was to investigate the effect of a school-based PA intervention on single and clustered cardiometabolic risk factors in 10-year-old children using a cluster randomized control trial (cluster-RCT). The intervention was conducted in a real-world setting and consisted of a curriculum-prescribed PA intervention delivered by classroom teachers.

2. Methods

2.1. Design and study population

The Active Smarter Kids (ASK) study was a seven-month cluster-randomized controlled trial conducted in November 2014 to June 2015 in western Norway (Resaland et al., 2015). Sixty invited schools (including at least seven children in each class) were randomized at a 1:1 ratio by a neutral and blinded third party, using a random number generator. After randomization, three schools (two intervention schools and one control school), withdrew from participation. In total, 1145 out of 1175 invited 5th graders from 57 schools agreed to participate, whereof valid data were obtained from 1129 children. The ASK study design, sample procedures and methods are described in detail elsewhere (Resaland et al., 2015) and will only briefly be presented herein.

2.2. Intervention

The PA intervention consisted of three components, consisting of 165 min of additional PA per week for the intervention children compared to the control children: 1) physically active academic lessons executed in the playground (3 × 30 min each week), 2) PA breaks during classroom lessons (5 min each school day), and 3) PA homework prepared by the teachers (10 min each school day). The intervention was a mandatory part of the school curriculum in intervention schools, adding to the existing mandatory curriculum-prescribed PA (45 min per week) and physical education (PE) (90 min per week), amounting to a total PA level of 300 min per week (60 min per day) of PA/PE. Control schools were encouraged only to provide the mandatory amount of PA/PE (135 min per week).

The intervention was delivered by the fifth grade classroom teachers. Three comprehensive pre-intervention seminars and two regional refresher meetings during the intervention period were conducted to empower, support and qualify the teachers to deliver the intervention. We aimed to provide activities that were inclusive and diverse to allow unfit or unenthusiastic children to experience mastery and enjoyment. Approximately 25% of the daily PA in school was intended to be of vigorous intensity; the children should be "*sweating and out of breath*".

2.3. Adherence to the protocol

On a monthly basis, school teachers reported the weekly amount of PA (duration in minutes and intensity) in a provided questionnaire. Intensity of PA was defined as 1 = low intensity, 2 = moderate intensity, and 3 = vigorous intensity. Intervention schoolteachers reported for all three components of the intervention (PA educational lessons, PA breaks, and PA homework).

2.4. Physical activity

Physical activity was measured by the ActiGraph GT3X+ accelerometer (ActiGraph GT3X+, LLC, Pensacola, Florida, USA). Children were instructed to wear the accelerometer on the right hip at all times over seven consecutive days, except during water-based activities, showering, or sleeping. Valid monitor wear-time was defined as reaching ≥480 min per day between the hours of 6:00 and 24:00 and a valid school-day as reaching ≥180 min per day between 9:00 and 14:00. Periods of ≥20 min of zero counts were defined as non-wear time (Esliger et al., 2005). Children having valid wear-time in ≥4 (out of 7) days and in ≥3 (out of 5) school days were included in the analysis. Previously established and validated cut-off points were used to define sedentary time (< 100 counts per min (cpm)), moderate-to-vigorous-intensity PA (MVPA) (> 2296 cpm) and VPA (> 4012 cpm) (Evenson et al., 2008; Trost et al., 2011). All accelerometer data were analyzed in 10-s epochs and 30 Hz using the KineSoft analytical software (KineSoft version 3.3.80, Loughborough, UK). Accelerometer data were collected at baseline (April–June 2014), midway through the intervention (January–February 2015) and at follow-up (April–June 2015).

2.5. Cardiorespiratory fitness

Cardiorespiratory fitness was measured using the validated Andersen shuttle-run test (Andersen et al., 2008; Aadland et al., 2014). Children ran 20 m between two lines in an intermittent pattern, touching the floor with one hand behind the line at each turn. They ran for 15 s and stood still for another 15 s. The test lasted for 10 min, where the total distance (meters) covered was used as an expression of CRF in the analyses. The performance in the Andersen test was converted into VO_{2peak} by the following equation; boys $VO_{2peak} = 27.1689 + (0.0397 \times \text{distance (m)}) - (0.1698 \times \text{body mass (kg)})$, girls $VO_{2peak} = 32.5793 + (0.0309 \times \text{distance (m)}) - (0.2351 \times \text{body mass (kg)})$ (Aadland et al., 2018).

2.6. Anthropometry

2.6.1. BMI

Body mass was measured to the nearest 0.1 kg using an electronic scale (Seca 899, SECA GmbH, Hamburg, Germany). A portable Seca 217 (SECA GmbH, Hamburg, Germany) was used to measure stature to the nearest 0.1 cm. Body mass index (BMI; $kg * m^{-2}$) was calculated as weight (kg) divided by the height squared (m^2).

2.6.2. Waist circumference

Waist circumference (WC) was measured using an ergonomic circumference measuring tape, Seca 201 (SECA GmbH, Hamburg, Germany). With the child's abdomen relaxed at the end of a gentle expiration, measures were taken between the lowest rib and the iliac crest to the nearest 0.5 cm. The mean of two measurements (≤1 cm) was used for analyses.

2.7. Blood sampling

A phlebotomist or nurse collected intravenous blood samples from the children's antecubital veins after overnight fast. Blood samples and serum were analyzed by an ISO-certificated laboratory for traditional

risk factors related to cardiometabolic diseases, such as insulin, glucose, triglycerides (TG), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and total cholesterol (TC). The TC:HDL-ratio was calculated to represent dyslipidemia. Insulin resistance was defined by the homeostatic model assessment (HOMA)-score = [insulin (pmol/L) * glucose (mmol/L)]/135 (Matthews et al., 1985).

2.8. Resting blood pressure

Systolic (SBP) and diastolic (DBP) blood pressure was measured by the Omron HEM-907 automated BP monitor (Omron Healthcare, Inc., Vernon Hills, IL, US). The device was previously validated according to the AAMI validation protocol (White and Anwar, 2001) and to the validation criteria of the international protocol for BP measuring devices (El Assaad et al., 2002). The children were measured in a quiet room after resting for 10 min in a seated position (without distractions) on the upper right arm. Four measurements were taken with one-min pauses in between, and the mean of the last three measurements was used for analysis. If the measurements differed by > 5 mmHg, a new measurement was taken, and the mean of the last four blood pressure measurements was used.

2.9. Maturity

Children self-assessed their puberty stage according to the Tanner scale (Tanner, 1962) using color pictures as proposed by Carel and Leger (Carel and Leger, 2008). We used breast and genital development for girls and boys, respectively, as a measure of pubertal stage. Category 1: prepubertal stage; category 2: first signs of puberty; categories 3–5: collapsed due to a small number of children representing more advanced pubertal stages than category 2, with category 5 being fully mature.

2.10. Demographic characteristics

We obtained self-reported educational level from the children's parents/legal guardians to assess socioeconomic status (SES). Education level was categorized into three groups using the highest educational level obtained by the mother or the father: i) upper or lower secondary school, ii) university < four years, and iii) university ≥ four years.

2.11. Ethics

The study protocol was approved by the South-East Regional Committee for Medical Research Ethics (2013/1893), and all procedures and methods adhered to the ethical guidelines of the World Medical Association's Declaration of Helsinki and its subsequent revisions (Assoc WM, 2013). Prior to commencement of the investigation, written informed consent was obtained from each child's parent(s) or guardian(s). The ASK study is registered in the Clinicaltrials.gov registry [NCT02132494].

2.12. Statistical analyses

All values exceeding five standard deviations from the mean were excluded before analysis. A continuous clustered risk score was calculated as the mean age-standardized z-scores of WC, SBP, TC:HDL-ratio, TG, HOMA-score, and CRF (inversed). The residuals of change between baseline and follow-up for the cardiometabolic risk factors were normally distributed, although some of the single cardiometabolic risk factors were skewed, and the respective risk variables were therefore not transformed.

Descriptive statistics are presented as the mean and standard deviation (SD), median and interquartile range (IQR), or frequency (%). Three analyses were used to evaluate the effect of the intervention, all conducted according to the statistical analysis plan (Resaland et al., 2015) and by using linear mixed models with school as a random effect to account for the cluster effect: 1) The effect of the intervention was investigated using intention-to-treat analysis, including all children who had valid data on the single cardiometabolic risk factors at both baseline and follow-up. Multiple imputations were also conducted for missing data, imputed from relevant variables using a Markov Chain Monte Carlo procedure. We assumed data were missing at random (Little et al., 2012). The models included group and baseline values as independent variables and change as the dependent variable. 2) Per-protocol analysis was conducted using similar models but only included data from intervention schools reporting ≥80% of prescribed PA and control schools reporting < 120% of the curriculum-prescribed PA (135 min/week). 3) In line with similar studies (Resaland et al., 2018a; Resaland et al., 2018b), we tested the moderating effects of cardiometabolic baseline values and sex. We hypothesized that intervention effects would be larger in girls, as they typically have lower levels of MVPA (Cooper et al., 2015) and CRF (Ruiz et al., 2016). The subgroup analyses were performed on children having valid measures in all cardiometabolic risk variables (n = 769) by including the following interaction terms in three separate analysis: a) group * tertile (tertiles were defined by baseline values in the clustered cardiometabolic risk score), b) group * sex, and c) group * sex * tertile. All models were full factorial models; two-way interaction models included main effects, and three-way interaction models included main effects and two-way interactions. The interaction effect by group * tertile (model a) and group * sex * tertile (model c) was investigated in linear mixed models using group, subgroup(s), and the interaction term as independent variables and change as the dependent variable. The moderating effect of group * sex (model b) also included baseline values of the single cardiometabolic risk factor as an independent variable in the respective models.

Analyses were performed using actual units and using z-scores to allow for a meaningful interpretation of results. All analyses were conducted using IBM SPSS version 25 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp., USA). A p-value < 0.05 was considered statistically significant in analysis of the main effects, whereas a p-value < 0.1 was applied to indicate statistical significance of interaction terms (Twisk, 2006). All data verification and cleaning was completed prior to the data-lock to avoid bias in the subsequent analyses.

3. Results

All schools were represented in the analysis (except in the per-protocol analysis). Some children did not provide data at either baseline or follow-up and were excluded from analysis as follows: WC (n = 8), SBP (n = 10), TC:HDL-ratio, TG and HOMA (n = 82 in each variable), CRF (n = 19), and clustered risk score (n = 99). Seven of the children dropped out during the intervention period (see flowchart in Fig. 1).

Table 1 shows the baseline characteristics of the intervention and control groups. In addition, Table A.1 (Appendix) shows the baseline characteristics of PA levels and sedentary behavior for girls and boys separately.

No significant intervention effects were found for any of the six cardiometabolic risk factors or the clustered risk score in either the intention-to-treat (Fig. 2) or the per-protocol analysis (Table 2). The effect sizes were very small in the intention-to-treat analyses for completers only (−0.07 to –0.01 SD units), for the imputed data (−0.06 to –0.01 SD units), and the per-protocol analysis (−0.05 to –0.001 SD units).

95% CI: 95% confidence interval; HDL: high-density lipoprotein; HOMA: homeostatic model assessment; ICC: intraclass correlation coefficient (school); INV: inverse; SD: standardized difference; SBP: systolic blood pressure; TC: total cholesterol; TG: triglyceride; WC: waist circumference.

Fig. 3 shows the difference in change in each cardiometabolic risk

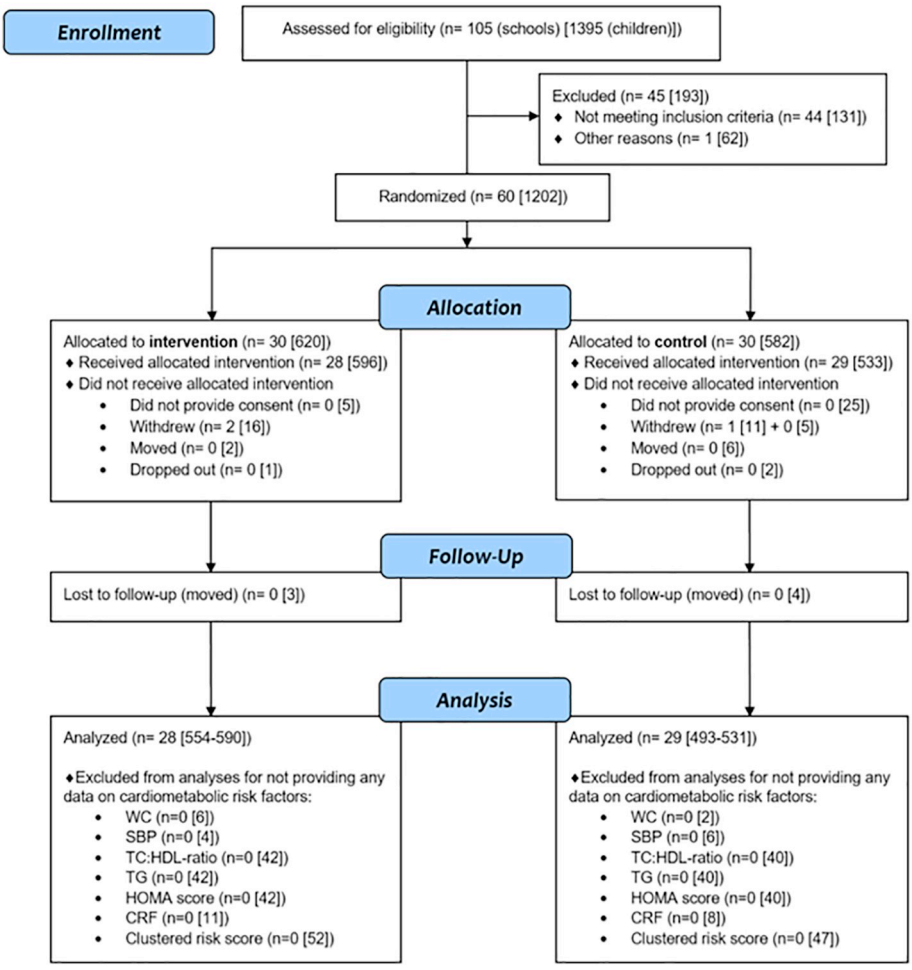

Fig. 1. Cohort flowchart of the enrollment, allocation, and follow-up of ASK children and final included population in the statistical analysis. The numbers in () and [] refer to the number of schools and the number of children, respectively.
Abbreviations: CRF: cardiorespiratory fitness; HDL: high-density lipoprotein; HOMA: homeostatic model assessment; TC: total cholesterol; TG: triglycerides; SBP: systolic blood pressure; WC: waist circumference.

factor between the intervention and control schools by tertiles (group*tertile), representing subgroups of children having the least favorable baseline values of clustered cardiometabolic risk factors in tertile 1 and the most favorable baseline values in tertile 3. A significant moderating effect by tertile was found for SBP (p for interaction = 0.07), TC:HDL-ratio (p for interaction = 0.03) and the clustered cardiometabolic risk score (p for interaction = 0.01).

The moderating effect of sex on the change in each cardiometabolic risk factor is shown in Fig. 4. A significant moderating effect for group * sex was found for WC (p for interaction = 0.03) and CRF (p for interaction < 0.001) in favor of the girls. In the stratified analysis, only CRF in girls reached significance and showed that CRF increased more from baseline to follow-up in girls from intervention schools (0.19 SD units) compared to girls from control schools.

No significant three-way interaction effects were found for any cardiometabolic risk factor or for the clustered risk score (p for interaction ≥0.25).

4. Discussion

We found no significant intervention effect of the ASK school-based PA intervention on any of the cardiometabolic risk factors or the clustered risk score in either the intention-to-treat or the per-protocol analysis in the total population. We did, however, find significant moderation by baseline cardiometabolic risk on SBP, TC:HDL-ratio and the clustered cardiometabolic risk score. Moreover, we found moderation by sex, showing a greater effect of the intervention on WC and CRF among girls compared to boys.

There were no significant intervention effects on children's PA or sedentary behavior in the total sample from baseline to follow-up, measured objectively by accelerometers (Resaland et al., 2016). High levels of PA in the control group may explain the lack of effect, which is not an unusual observation in PA intervention trials (Waters et al., 2012). Furthermore, the high baseline levels of PA in the ASK study could indicate a potential ceiling effect in most children. ASK children from both the intervention schools and control schools were, on average, more physically active than population-based samples of 9–10-year-old Norwegian children (Health TNDo, n.d.) as well as European and US children (Cooper et al., 2015). Since the premise in the ASK study was that increased PA would cause a change in cardiometabolic risk factors (including CRF), this is likely to be the main reason why we were unable to detect measurable benefits on any of the cardiometabolic risk factors. Another reason could also be that the intervention potential, with respect to the cardiometabolic risk factors, was relatively low, as children have generally healthy cardiometabolic risk scores (Stavnsbo et al., 2019). Furthermore, we found no difference in cardiometabolic risk factor levels at follow-up between children from intervention and control schools in the per-protocol analysis. The per-protocol analysis only excluded one intervention school, while 13 control schools were excluded because they proved too much PA. It

Table 1
Baseline characteristics of intervention and control school children.

	N	Intervention	N	Control
		Mean (± SD)/median [Q1-Q3]/n (%)		Mean (± SD)/median [Q1-Q3]/n (%)
Age (yr)	596	10.2 (0.3)	533	10.2 (0.3)
Height (cm)	579	142.6 (6.8)	517	142.8 (6.8)
Weight (kg)	578	36.9 (8.0)	517	37.2 (8.1)
Puberty (tanner)	569		512	
Stage 1		170 (30)		139 (27)
Stage 2		330 (58)		318 (62)
Stage 3–5		69 (12)		55 (11)
Parents' education level	578		491	
≤Upper secondary school		179 (31)		172 (35)
< 4 years of university		179 (31)		142 (29)
≥4 years of university		220 (38)		177 (36)
Physical activity (school day)	538		538	
Total PA (cpm)		650 (186)		641 (192)
MVPA (min/day)		29 (11)		28 (10)
SED (min/day)		179 (20)		179 (21)
Physical activity (full day)	542		464	
Total PA (cpm)		745 (299)		723 (257)
MVPA (min/day)		77 (28)		74 (24)
SED (min/day)		468 (57)		468 (60)
% achieving PA guidelines		71		70
Cardiometabolic risk factors				
BMI (kg/m^2)	578	17.5 [15.9–19.5]	517	17.2 [16.0–19.6]
WC (cm)	577	60.3 [56.0–65.5]	517	60.3 [57.0–65.7]
SBP (mm hg)	575	105.5 (8.3)	511	105.2 (8.7)
DBP (mm hg)	575	58.2 (5.8)	511	57.5 (6.7)
LDL cholesterol (mmol/L)	532	2.5 (0.7)	471	2.5 (0.6)
HDL cholesterol (mmol/L)	533	1.6 (0.3)	471	1.6 (0.3)
Total cholesterol (mmol/L)	533	4.4 (0.7)	471	4.5 (0.7)
TC:HDL-ratio	533	2.8 [2.4–3.3]	471	2.8 [2.4–3.2]
TG (mmol/L)	533	0.69 [0.55–0.89]	471	0.68 [0.55–0.89]
Glucose (mmol/L)	533	5.0 (0.3)	471	5.0 (0.3)
Insulin (pmol/L)	532	49.5 [35.3–68.2]	470	49.2 [35.1–66.8]
HOMA-score	532	1.8 [1.3–2.5]	470	1.8 [1.3–2.5]
Andersen (m)	550	893.6 (102.6)	495	891.9 (103.7)
Estimated VO_{2peak} (mL/kg/min)	549	54.2 (5.5)	495	54.0 (5.6)
Clustered risk score*	484	0.004 (0.66)	429	−0.005 (0.63)

Abbreviations: BMI: body mass index; cpm: counts per min; CRF: cardiorespiratory fitness; DBP: diastolic blood pressure; HDL: high-density lipoprotein; HOMA: homeostatic model assessment; LDL: low-density lipoprotein; MVPA; moderate-to-vigorous physical activity; PA: physical activity: SBP: systolic blood pressure; SED: sedentary; TG: triglyceride. Risk variables in *italics* were skewed (nonnormal distribution). Values for PA were adjusted for valid wear time. PA guidelines represent children who achieved a mean minimum of 60 min/day of MVPA. *The clustered risk score based on the following six cardiometabolic risk variables: WC, SBP, TC:HDL-ratio, TG, HOMA-score, and CRF (inversed).

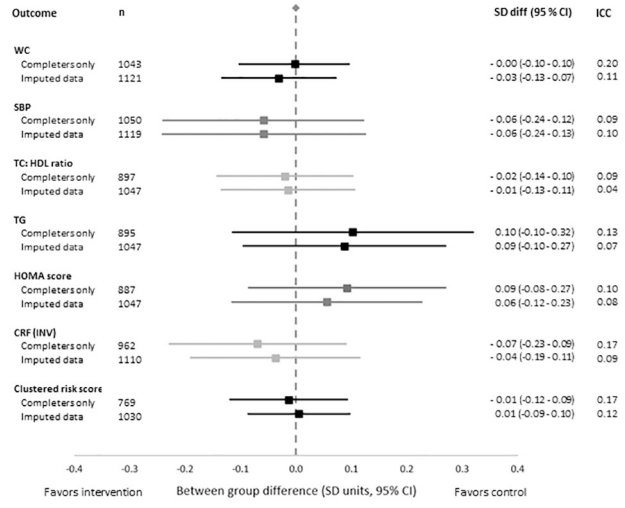

Fig. 2. The intervention effect (intention-to-treat analysis) from completers only (n = 769–1050) and from imputed data (N = 1030–1121) for those children having a valid measure at either baseline or follow-up. Effect sizes are presented in standardized units (SD) and 95% confidence interval. Cardiorespiratory fitness was inversed (CRF*-1).

Table 2
Effects of the intervention on cardiometabolic risk factors (per-protocol analysis).

	n	Group difference, β (95% CI)	*p*-value	ICC
WC	831	0.01 (−0.85 to 0.87)	0.98	0.19
SBP	833	−0.23 (−2.00 to 1.53)	0.79	0.09
TC:HDL-ratio	727	−0.02 (−0.11 to 0.08)	0.71	0.08
TG	727	0.03 (−0.03 to 0.10)	0.32	0.10
HOMA-score	718	0.14 (−0.14 to 0.42)	0.32	0.11
CRF	769	–0.05 (−17.71 to 17.62)	0.97	0.14
Clustered risk score	624	−0.003 (−0.11 to 0.10)	0.95	0.14

Abbreviations: 95% CI: 95% confidence interval; β: beta-coefficient; CRF: cardiorespiratory fitness; HDL: high-density lipoprotein; HOMA: homeostatic model assessment; ICC: intraclass correlation coefficient (school); TC: total cholesterol; TG: triglyceride; SBP: systolic blood pressure; WC: waist circumference. Per-protocol: intervention schools reporting ≥80% of prescribed PA and control schools reporting < 120% of the curriculum prescribed PA.

seems plausible that overestimation of PA levels from intervention school teachers could have occurred, since no difference was found in accelerometer data (Resaland et al., 2016). Alternatively, control schools might have increased their activity levels, due to an increased interest in PA in response to project information, testing etc.

Children with the less favorable baseline values in the clustered risk

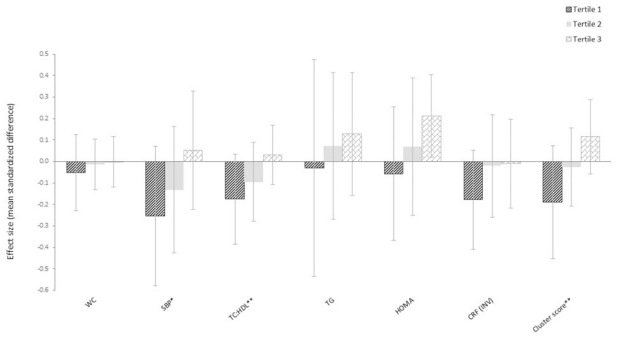

Fig. 3. Subgroup differences between the intervention and control group by tertiles (tertile 1 is the least favorable group and tertile 3 is the most favorable group in the clustered risk score at baseline). Effect sizes are presented in standardized units (SD) ± 95% confidence interval (CI). The subgroup (n = 769) of children had valid measures in all cardiometabolic risk variables. Cardiorespiratory fitness was inversed (CRF*-1). The clustered risk score consisted of the following variables; WC, SBP, TC:HDL-ratio, TG, HOMA-score and CRF (inversed).
*Significant group * tertile interaction ($p < 0.1$). **Significant group * tertile interaction ($p < 0.05$).

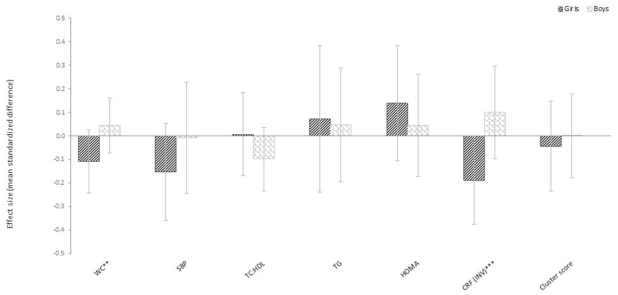

Fig. 4. Subgroup differences between the intervention and control groups by sex. Effect sizes are presented in standardized units (SD) ± 95% confidence interval (CI). The subgroup (n = 769) of children had valid measures in all cardiometabolic risk variables. Cardiorespiratory fitness was inversed (CRF*-1). The clustered risk score was based on the following variables: WC, SBP, TC:HDL-ratio, TG, HOMA-score and CRF (inversed).
*Significant group * sex interaction ($p < 0.1$). **Significant group * sex interaction ($p < 0.05$). ***Significant group * sex interaction ($p < 0.001$).

score (tertile 1) benefitted more from the PA intervention than children with more favorable values. Although no stratified analyses of the intervention effect by tertiles reached statistical significance, there was a consistent pattern of mean effect sizes in favor of the children in tertile 1, supporting findings from a previous school-based PA intervention study (Resaland et al., 2018a). Post hoc analysis investigating accelerometer data measured midway through the ASK intervention period showed a significant moderating effect by tertile on sedentary time during all day. In the stratified analysis, children in tertile 1 were significantly less sedentary than their peers from control schools (Appendix, Fig. A.1). Although cardiometabolic risk factors might be more influenced by e.g. higher MVPA time than sedentary time per see (Ekelund et al., 2012), reducing time spent sedentary do reveal more time to be physical active and has shown beneficial effects on cardiometabolic health in children (Tremblay et al., 2011). No other midway analysis reached significance, but the all-day PA levels reflect the consistent pattern observed of changes in favor of the group of children having the least favorable baseline cardiometabolic risk profile. In addition, when comparing cardiometabolic risk factor levels with international age- and sex specific reference values (39), tertile 1 had a mean standardized difference in the clustered risk score of 0.52 SD (95% CI 0.47 to 0.58). Although less favorable, the clustered risk score was only moderately higher than the international reference values, which could indicate that children in the ASK study, even with the most unfavorable risk profile, were within healthy cardiometabolic ranges and had a relatively low potential to change.

The subgroup analysis revealed significant interaction effects by sex on WC and CRF in favor of the girls. Furthermore, girls from the intervention schools increased their CRF levels significantly more between baseline and follow-up than girls from control schools. Since girls' CRF levels have shown to stagnate or even decrease after the age of nine (Stavnsbo et al., 2018), this is a positive outcome of the intervention. Sex-specific differences on outcomes in school-based PA interventions have been a controversial issue. However, some evidence exist of girls responding better to in school PA than boys (Pangrazi et al., 2003). In a recent review of the effect of school-based RCT PA interventions on CRF, a significant increase in CRF was found among girls but not among boys (Pozuelo-Carrascosa et al., 2017). To better understand the different responses in girls and boys observed in the present study, we performed post hoc analysis of the midway accelerometer data (Appendix, Fig. A.2). The analysis showed significant interaction effects by sex on total PA, MVPA and VPA both during school and all day in favor of the girls. Compared to girls from control schools, girls from intervention schools were significantly more physically active in total, did more VPA and were less sedentary during school hours. In accordance with studies showing that boys engage in more PA and are less sedentary than girls (Cooper et al., 2015), girls at baseline in the ASK study had significantly lower total PA levels, were less in MVPA and VPA, and were more sedentary both during school and all day than the boys (Appendix, Table A.1). Furthermore, girls had lower levels of CRF and in general a less favorable risk profile than boys at baseline (Stavnsbo et al., 2019). Thus, the girls had a larger potential for change as a response to the PA intervention than the boys, which plausibly can explain the positive outcomes.

PA interventions in school children have shown conflicting results with respect to effects on cardiometabolic risk factors, although with some indications of higher success in improving fitness levels (Sun et al., 2013; Dobbins et al., 2013; Kriemler et al., 2011; Pozuelo-Carrascosa et al., 2017) rather than the *traditional* cardiometabolic risk factors such as adiposity, blood pressure, glucose intolerance, and dyslipidemia (Sun et al., 2013; Dobbins et al., 2013). Exploring intervention effects in generally healthy young children is demoing, since the intervention potential is limited. Thus, future studies should consider to investigate effects on cardiometabolic risk factors in both groups and subgroups of children with a less favorable risk profile at baseline, including sex specific analysis, as done in the present study.

4.1. Strengths and limitations

The cluster-RCT design is a major strength of the study since it limits bias in treatment assignment, such as selection bias and confounding, and allow for investigating the effect of increased PA in a pragmatic, real-world setting. To minimize treatment contamination between trial arms, cluster randomization on a school level was advocated over randomization on an individual- and class level within schools. The intervention was delivered by the classroom teachers, which increases the external validity of the study. Other strengths are the objectively measured PA, the relatively large sample size and low attrition rate.

The results should be generalized with caution, as the sample only represents one county in Norway. The ASK intervention was designed to first and foremost affect the main outcome, academic performance, and the daily dose and intensity of PA needed to improve cardiometabolic risk factors may differ. The intervention period of 7 months may have been insufficient and the intensity too low to positively affect all cardiometabolic risk factors. Furthermore, the weekly PA reports were completed by the school teachers, which might have introduced subjective errors in the per-protocol analysis. Another limitation is that the ASK study investigated a group of children with a generally low intervention potential due to initial high PA levels. Also, the ASK study

did not record food intake, but the randomized design should have countered any confounding effect of diet.

5. Conclusion

The present study found no significant intervention effect of active academic classes and short active breaks during school hours on children's cardiometabolic health in the overall sample. However, subgroup analysis showed that girls had a greater effect of the intervention on WC and CRF than boys, and the data indicate that PA interventions in school can contribute to better cardiometabolic health in those subgroups of children that have the less favorable cardiometabolic risk profiles at baseline.

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Declaration of competing interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ypmed.2019.105868.

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