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Clustered cardiovascular disease risk factors track from childhood to adolescence

Running title: Tracking of clustered CVD risk in youth

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Abstract

Background: Clustering of cardiovascular disease (CVD) risk factors has been found in children as young as 9 years of age. However, the stability of this clustering over the course of childhood has yet to be determined. The purpose of this study was to determine tracking of clustered CVD risk from young school-age through adolescence and examine differences in tracking between levels of overweight/obesity and cardiorespiratory fitness (VO_{2peak}). Methods: Six year-old children (n = 434) were measured three times in 7 years. Anthropometrics, blood pressure and VO_{2peak} were measured. Fasting blood samples were analyzed for CVD risk factors. A clustered risk-score (z-score) was constructed by adding sex-specific z-scores for blood pressure, homeostatic model assessment (HOMA-IR), triglyceride, skinfolds and negative values of HDL-cholesterol and VO_{2peak}. Results: Significant tracking coefficients were found between clustered z-score at all time intervals ($r = 0.514$, 0.559 and 0.381 between ages 6 to 9, 9 to 13 and 6 to 13 years, respectively, all $P< 0.0001$). Tracking was higher for low-fit children, whereas no clear pattern was found for different levels of body-fat. Conclusions: We found that clustered z-score is a fairly stable characteristic through childhood. Implementation of preventive strategies could therefore start at early school-age.

Introduction

"High risk" for future cardiovascular disease (CVD) is difficult to define in children, as no hard endpoints such as manifest disease or death has yet occurred. Clustering of individual risk factors in the same individual has been suggested as a good method to assess CVD risk level in apparently healthy children, as it describes a state where several risk factors are high simultaneous in the same individual (1). Earlier studies from our group found no clustering of CVD risk factors in 6 year old children in this cohort, whereas at age 9 years three or more CVD risk factors was found in 3.33 times as many participants than expected, which corresponded to 13.8 % of the population (2). However, clustering of CVD risk factors in children is only of interest if it is a stable characteristic. Tracking is a term used to describe the development of a characteristic over time and involves both the longitudinal stability of this variable and the ability of one measurement to predict the value of following measurement(s) (3). A recent review of the literature regarding tracking of CVD risk factors from childhood to adulthood conclude that despite the differences in methodology, studies have consistently found tracking of cardiometabolic risk factor clustering from childhood or adolescence to adulthood (4). However, the researchers concluded that the shorter-term stability of clustered risk factors over the course of childhood and adolescence has yet to be elucidated. Knowledge about this stability is potentially important, as it might demonstrate whether there is an optimal time-point in childhood to measure health variables and possibly initiate interventions. Furthermore, clustering of CVD risk factors in children have been found associated with lifestyle factors such as obesity (1,5-8) and cardiorespiratory fitness (VO_{2peak}) (1,7-9). To our knowledge only one study in youth has examined the effect of obesity on tracking of clustered risk (10) and no studies have looked at the effect of VO_{2peak}. Therefore, the aim of this study was to evaluate tracking of clustered CVD risk in youth using three time-points from

age 6 to age 13 years. Secondly, to examine how different levels of overweight/obesity and VO_{2peak} affect the precision of tracking.

Methods

Subject for this study were participants in The Copenhagen School Child Intervention Study (CoSCIS), which was started in 2001 and included all children attending kindergarten class in two communities in the area of Copenhagen (46 kindergarten classes in 18 public schools). Written informed consent was obtained from the parents/guardian of 706 children (69% of the population) and 696 actually participated in the study at baseline. Following the intervention, the children were re-tested in 2004/2005 at age 9 years and followed-up again in 2008 at age 13 years. The study has been described in details elsewhere (11-13). In the present analysis we included all children with complete measures of CVD risk factors at least at two of the three time-points (n = 434). The study was approved by the ethical committee, University of Copenhagen.

Since the complete methodology has been previously published, the methodology presented here includes only those variables of interest. Height and body weight were measured according to standard procedures. Body mass index (BMI) was calculated ($kg \cdot m^{-2}$) and BMI z-scores (zBMI) were computed based on WHO recommendations (14). Bicipital, tricipital, subscapular and suprailiac skinfolds were measured using standard procedures with a Harpenden skinfold caliper (Harpenden, West Sussex, UK). The sum of the four skinfolds (S4SF) was used as a measure of body fatness (15).

Cardiorespiratory fitness (VO_{2peak}) was assessed using a continuous running protocol on a treadmill until exhaustion. VO_{2peak} was measured directly on an AMIS 2001 Cardiopulmonary Function Test System (Innovision, DK 5260 Odense) at age 6 and 9 years and using the COSMED K4b^2 portable metabolic system (COSMED, Rome, IT) at age 13 years. Both systems provide valid measures of VO_2

when validated against the Douglas bag method (16,17). Detailed criteria for an accepted test has been reported earlier (12). Blood pressure was measured in the sitting position after 15 minutes of rest with a Dinamap XL vital signs blood pressure monitor (Critikron, Inc., Tampa, FL) using appropriate sized cuffs. The mean of the last three of 5 measurements taken over 10 minutes was used for analysis. Fasting blood samples were taken between 08:00 – 09:30 h and glucose was analyzed immediately (Hemocue, Sweden). The remainders of the samples were centrifuged; plasma aliquoted within 30 min, kept at -20°C, and later stored at -80°C until analyzed. Insulin was analyzed spectrophotometrically using an enzyme linked immunosorbent assay (DAKO Insulin, Code no. K6219). Insulin resistance was estimated according to homeostasis model assessment (HOMA-IR) as glucose (mmol·1^{-1}) multiplied by insulin (mU·1^{-1}) divided by 22.5 (18). Blood lipids were analyzed on a COBAS FARA (Roche, Switzerland) using spectrophotometry (ABX diagnostics, Montpellier, France).

Statistical analysis

A composite CVD risk score (clustered z-score) was constructed by adding the sex-specific z-scores for systolic blood pressure, HOMA-IR, triglyceride (TG), S4SF and the negative z-scores for high-density lipoprotein cholesterol (HDLc) and VO$_{2peak}$. Rationale for choosing these variables for the clustered z-score has been described elsewhere (19). In analysis with stratification for S4SF, S4SF was removed from the clustered z-score and in analysis with stratification for VO$_{2peak}$, this variable was removed from the clustered z-score.

No differences in the clustered z-score between intervention and control group of the CoSCIS was evident (11), so the groups were pooled for all analyses. For descriptive purposes means and standard deviations for all variables at age 6, age 9 and age 13 years were computed. BMI, S4SF, HOMA-IR and TG were positively skewed and therefore transformed (natural log) for the analyses. Tracking coefficients were calculated between the clustered z-score at age 6 to 9 years, age 6 to 13 years and age

9 to 13 years using Pearson correlations (3). This was also done for each of the CVD risk factors, to determine which factors were the most important in the tracking of the clustered z-score. High risk cases were defined as having a clustered z-score above 1 standard deviation (SD) corresponding to ~ 16, 14 and 12 % of the population at ages 6, 9 and 13 years, respectively. This choice of assigning high-risk was based on an earlier study by Andersen et al. (19) indicating that a clustering of CVD risk factors, defined as being in the least favorable quartile of four or more risk factors, was found in around 11% of a normal European pediatric population. This group was characterized by the fact that risk factors were not independently distributed, or in other words, they clustered. The authors of that study therefore defined 1 SD above the mean in summed Z score to be at risk, which was higher than the actual calculation (16 %) (19). We chose to use the same risk cut-point, even though it is arbitrary, as no evidence exists regarding a biologic cut-point over which CVD risk increases for these age groups. Logistic regression analysis was performed and odds ratios between children in three different risk categories; low risk (< median z-score), moderate risk (median to 1 SD) and high risk ($\geq$ 1 SD) at one time-point for being at high risk at the second time-point. Finally, to evaluate the influence of VO_{2peak} and fatness (S4SF), children were grouped in tertiles based on these variables and clustered z-score (without VO_{2peak} or S4SF, respectively) tracking coefficients were calculated within each tertile using Pearson correlations. All analyses were performed using the Statistical Package for the Social Sciences version 19 (SPSS, Chicago, IL).

Results

The general characteristics of the sample at the age of 6, 9 and 13 years are presented in Table 1. BMI, S4SF, systolic blood pressure and HOMA-IR increased with age. VO_{2peak} increased from age 6 to age 9

years, triglycerides increased from age 9 to age 13 years and HDLc increased from age 6 to age 9 years and then decreased from age 9 to age 13 years. Tracking coefficients between clustered z-score at age 6 to 9 years, 9 to 13 years and 6 to 13 years are presented in Table 2. Moderate correlations were found between clustered z-score at age 6 to 9 years and 9 to 13 years, whereas the coefficient between age 6 and 13 years was somewhat weaker. These coefficients did not change significantly when analyses were done for each sex separately (data not shown). For the single risk factors highest tracking coefficients were seen for S4SF, followed by systolic blood pressure and HDLc. Tracking coefficients for HOMA-IR and TG were low to moderate. The tracking coefficients for VO_{2peak} were high from 6 to 9 years and 9 to 13 years, but low from 6 to 13 years.

Logistic regression showed that children with moderate and high risk, respectively, in clustered z-score at first time-point had a 6.1 and 21.2 times greater risk, respectively, of having a clustered z-score above 1 SD at the second time-point between the ages 6 to 9 years, 4.5 and 30.8 times greater risk between the ages 9 to 13 years, and 2.3 and 4.9 times greater risk between the ages 6 to 13 years, compared to children with low risk in clustered z-score (Table 3).

When children were grouped based on their level of VO_{2peak}, tracking coefficients were higher in the 1st tertile (least fit) at all three time intervals (*r*-values 0.50-0.67). The coefficients were strong in the 1st and 2nd tertiles and low in the 3rd tertiles (*r*-values 0.25-0.39). When children were grouped based on their S4SF, we found lowest tracking coefficients in the 1st tertile (least fat) at all three time intervals. However, the picture was not as clear as for VO_{2peak}. Between age 6 and 9 years there was no significant coefficient in the 1st tertile (*r*-value 0.068), a strong coefficient in the 2nd tertile (*r*-value 0.499) and moderate coefficient in the 3rd (*r*-value 0.34). Between age 6 and 13 years the coefficients were weak in all tertiles (non-significant in the first) (*r*-values 0.20, 0.31 and 0.23 in 1st, 2nd and 3rd

tertile, respectively). Between age 9 and 13 the coefficients were weak in the 1st and 2nd tertile (r-values 0.32 and 0.30) and stronger in the 3rd (r-value 0.49).

Discussion

The present study examined the short-term tracking of a clustering of CVD risk factors in a normal youth population from early school-age to start adolescence. We found moderate to high level of tracking between all the measured time points and the risk of having a high sum of z-score at a second time point was between 2.3 and 30.8 times increased for children having a high sum of z-score at the first time point. Similarly, the only other study examining the stability of clustered CVD risk factors from childhood (age 9 years) to adolescence (age 15 years) in a sample of Swedish and Estonian children found moderate overall tracking coefficient for boys and girls, respectively (20). Also studies looking at clustered CVD risk factor tracking from childhood or adolescence to adulthood displayed similar results (21-24). As CVD risk factors did not cluster at age 6 years in this cohort (25), it was unexpected to find a high degree of tracking between the ages 6 to 9 years and 6 to 13 years. The results indicate that a relatively high level of several CVD risk factors, even though they were independently distributed (no clustering), at this low age, is predictive for future high metabolic risk. Juhola and colleagues (26) using data from the Cardiovascular Risk in Young Finns Study, investigated sensitivity and specificity rates for predicting abnormal CVD risk factors as an adult from values obtained at ages 3, 6, 9, 12, 15 and 18 years. They found that for obesity and blood pressure values at all childhood ages were predictive for the adult value. For HDLc there was no difference between age groups for females, but for males HDLc levels at ages 6, 9 and 12 years were most predictive for adult values, compared to ages 3, 15 and 18 years. All together these results suggest that CVD risk factors level is a fairly stable characteristic from early childhood to adulthood. We did not find any sex

differences in tracking of clustered CVD risk (data not shown), which is similar to results from some (20,21), but not all studies (27).

In the present study all of the single risk factors included in the summed z-score had a positive tracking coefficient (Table 2), which means that they all contributed to the tracking coefficient for the sum of z-score. However, tracking coefficients of single risk factors varied from low to high, whereas the tracking coefficients for the clustered z-score varied from moderate to high. In agreement with our findings, Bao and colleagues (24) found that tracking expressed as an inter-age correlation was higher for a clustered risk score ($r = 0.64$) compared to the single risk factors ($r = 0.34$-0.57); conversely, others did not find this difference between individual and clustered risk factors (21,22). Based on these results, there is no indication of a much higher tracking of a clustered risk score, compared to the single risk factors. We do not have any explanation for this, as we expected to find a substantial higher tracking of the clustered Z-score because of the advantages of this score (see below).

Clustering of CVD risk factors have been found related to VO_{2peak} in cross-sectional studies in youth (1,7,9,23,28). We analyzed the stability of the summed CVD risk factors within each tertile of VO_{2peak} and found that a lower baseline VO_{2peak} level was associated with a higher tracking coefficient of clustered z-score and this was consistent for all time intervals. This implies that within the least fit group, the stability of metabolic health is greater compared to within the most fit group. Conjecture suggests that it takes more effort to positively change health affecting behavior (e.g. lose weight or increase physical activity and fitness) compared to change behavior in a way that negatively influence your health (e.g. by gaining fat and decreasing physical activity). To our knowledge, no other studies have examined the effect of VO_{2peak} level on the degree of tracking of clustered CVD risk factors in this age group and our results should therefore be verified in other cohorts.

In the present study, when children were grouped based on their S4SF no clear picture was found between groups in tracking of clustered CVD risk factors. This could suggest that the level of fatness may not be pivotal for the stability of CVD risk factor clustering over time in a normal youth population. This is not to say, that overweight does not play an important role in the development of clustering of risk factors, a fact that has been demonstrated in several studies. In cross-sectional studies overweight and obesity have consistently been found related to clustering of CVD risk factors in children and adolescents (1,5-7) and convincing evidence suggests that overweight and obesity tracks from childhood into adulthood (29). Furthermore, some studies have found that overweight or obesity in childhood is associated with increased risk of later development of CVD risk factor clustering (30,31). However, in one of these studies, the association disappeared when fatness was removed from the clustered risk score. Thus, the authors concluded that the effect of fatness in childhood on the cluster of CVD risk factors in adolescence is a result of adiposity tracking (30). In support of this, a recent review concludes that there is not much evidence for childhood obesity to be an independent risk factor for adult CVD risk, because the relationship is attenuated or no longer present when adjusting for adult obesity (32). Likewise, Chen and co-workers demonstrated that longitudinal changes in clustering of CVD risk factors assessed by incremental area (area under the curve) were decreased by approximately 50%, when adjusted for BMI (10). These results suggest that fatness is an important part of a causal chain leading to clustered CVD risk. It is however, not possible to conclude anything about causation; it could be that fatness is an intermediate and adjusting for an intermediate may remove the associations between the investigated exposure and the outcome.

The strength of this study is the relatively large cohort followed for a 7 years period with three measurements from early school-age to start adolescence. The quality of included measurements, e.g. the direct measurement of VO_{2peak}, is a strength of the study. Also the inclusion of the clustered Z-score

is strengthening the study. As stated earlier, this type of outcome may be a better indicator of health in apparently healthy children and adolescents, compared to the individual risk factors, as it uses all available information (no cut-points, but a continuous score). Furthermore, a clustered score can to some extent compensate for the day-to-day fluctuations in the individual risk factors, and it is not as sensitive to measurement errors. However, this method also has some limitations. First, no consensus exists regarding which risk factors to include in the score or how to define 'high risk'. Therefore, the risk is specific to the study sample only and is not based upon a biologic measure. Second, the clustered z-score is based upon the assumption that all included individual CVD risk factors are equally important in defining CVD risk, which may not be the case. However, there is no evidence suggesting how risk factors should be weighed, and we may never get that in children, because no one have manifest CVD. Another limitation of this study is the relatively lean and healthy population studied which could limit the generalizability of the results especially to more overweight and metabolic impaired populations. However, as mentioned, we have previously found that in this cohort CVD risk factors cluster in ~ 14 % of the children already from the age of 9 years, and that this cluster is related to VO_{2peak} and fatness (2). Another factor possibly influencing our results is the drop-out of the study. This drop-out has been described in details elsewhere (11). Briefly, it was shown that there were no significant differences in 6 years values of BMIz, waist circumference or VO_{2peak} between children who participated at age 9 years and children who dropped out. However, children participating at age 13 years had significantly lower baseline zBMI and waist circumference and a higher baseline VO_{2peak} compared to the children who dropped out of the study. This is also apparent from the results in zBMI seen in table 1, where the value is lower at age 13 years compared to age 6 and 9 years, implying that the fattest participants have dropped out. Furthermore, the drop-out is larger in some variables e.g. VO_{2peak} and blood variables because of the strict inclusion criteria and invasive character of these

measurements. Therefore, the number of subjects included in analysis of these variables and the clustered z-score is considerably less compared to e.g. S4SF. Finally, the size of the tracking coefficient is highly dependent upon the reproducibility of the measurement and its error variation. In that regard S4SF is easier to reproduce compared to some of the other variables measured, e.g. VO_{2peak}. Also, as described above, the clustered z-score is easier to reproduce than some of the individual risk factors.

In conclusion, moderate to strong tracking was found for clustered z-score in a normal pediatric population measured three times from age 6 to age 13 years. Furthermore, children with a higher clustered z-score at first measurement had an increased risk of having a clustered z-score above 1 SD at the second measurement. This means that a high level in several CVD risk factors in early school-age is already predictive for the development of the clustering of CVD risk factors seen in the older age-groups. Tracking of clustered z-score differed between tertiles of fitness with children in the lowest fitness group displaying the highest tracking coefficients. The picture was not as clear for tertiles of fatness. We believe that the results of the present study have important clinical implications, as they show stability of clustering of CVD risk factors across school-age and points to implementation of preventive strategies starting in early childhood.

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Table 1. Physical characteristics of participants by age.

Variables	Age 6 years mean (SD) n = 434	Age 9 years mean (SD) n = 433	Age 13 years mean (SD) n = 352
Age (years)	6.76 (0.35)	9.56 (0.36)	13.37 (0.34)
BMI (kg·m^2)	15.90 (1.58)	17.06 (2.20)	19.11 (2.74)
zBMI for age	0.21 (0.94)	0.22 (1.02)	-0.05 (1.05)
Sum of 4 skinfolds (mm)	25.70 (8.23)	31.66 (14.30)	34.73 (17.29)
VO$_{2peak}$ (ml·kg^{-1}·min^{-1})	46.97 (5.94)	49.80 (6.99)	49.17 (8.36)
Systolic Blood Pressure (mmHg)	97.31 (7.35)	103.45 (8.47)	110.35 (8.63)
Insulin resistance (HOMA-IR)	0.79 (0.67)	1.27 (0.68)	2.78 (1.55)
HDLc (mmol·l^{-1})	1.49 (0.26)	1.60 (0.33)	1.46 (0.32)
TG (mmol·l^{-1})	0.59 (0.24)	0.55 (0.24)	0.79 (0.35)
Clustered Z-score	-0.19 (2.92)	-0.25 (3.34)	-0.09 (3.48)

SD: standard deviations, BMI: body mass index, zBMI: mmHg: millimetre of mercury, HOMA-IR: homeostatic model assessment, HDLc: high-density lipoprotein cholesterol, TG: triglyceride.

Table 2. Tracking coefficients or Pearson correlations (r) between clustered z-scores and the single risk factors at different ages.

	6 to 9 years		9 to 13 years		6 to 13 years	
	n	*r*	*n*	*r*	*n*	*r*
Clustered Z-score	322	0.514	262	0.559	254	0.381
Sum 4 skinfolds	429	0.858	348	0.774	347	0.668
VO_{2peak}	398	0.524	314	0.561	306	0.294
Systolic BP	430	0.538	347	0.499	349	0.441
HOMA-IR	357	0.317	293	0.213	298	0.248
HDLc	362	0.347	297	0.686	301	0.414
TG	359	0.230	297	0.327	298	0.195*

All *P*-value < 0.0001, unless marked. *: *P*-value = 0.001

VO_{2peak}: cardiorespiratory fitness, BP: blood pressure, HOMA-IR: homeostatic model assessment, HDLc: high-density lipoprotein cholesterol, TG: triglyceride.

Table 3. Risk of high clustered z-score (above 1 SD) based on former risk level of clustered z-score.

	Odds ratio	95% CI	p-value
Age 6 to 9 years			
Low risk at age 6 years	1		
Moderate risk at age 6 years	6.10	2.37- 15.67	<0.0001
High Risk at age 6 years	21.22	7.93-56.80	<0.0001
Age 9 to 13 yrs			
Low risk at age 9 years	1		
Moderate risk at age 9 years	4.51	1.71-11.89	0.002
High Risk at age 9 years	30.80	9.73-97.50	<0.0001
Age 6 to 13 yrs			
Low risk at age 6 years	1		
Moderate risk at age 6 years	2.32	1.04-5.19	0.040
High Risk at age 6 years	4.86	1.92-12.34	0.001

Low risk ($\leq$ median), moderate risk (> median < 1SD) and high risk ($\geq$ 1SD). Low is set as reference.