REVIEW ARTICLE

Tracking of cardiometabolic risk factor clustering from childhood to adulthood

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Abstract
Cardiometabolic risk factor clustering is predictive of future cardiovascular disease. If clustering of risk factors is a stable characteristic from childhood to adulthood, then intervention in high-risk children may provide an early opportunity to decrease the progression to overt cardiovascular disease outcomes. Thus, the purpose of this paper was to review the evidence for risk factor clustering being a stable characteristic from childhood to adulthood. Seven articles were identified that met the inclusion criteria. Despite varying definitions of risk factor clustering and different methodologies for assessing tracking, the results generally showed stability of risk factor clustering from childhood into adulthood. Inter-age correlations of risk factor cluster scores ranged from 0.42 to 0.67, and the proportions of individuals remaining in the upper quantiles of risk over time were significantly greater than predicted by chance alone. Future studies are needed to elucidate the effects of gender, ethnicity, and lifestyle behaviors on the tracking of risk factor clustering.

Key words: Cardiovascular risk factors, clustering, longitudinal studies, metabolic syndrome, tracking

Background
Cardiometabolic risk factors tend to cluster as a constellation of abnormal metabolic, lipid and non-lipid variables in some individuals. The metabolic syndrome is one definition of risk factor clustering; however, its classification and diagnosis is challenging due to the existence of several different operational definitions in both adults (1) and children (2). Despite the lack of a standardized definition, metabolic syndrome prevalence ranges from 2–9% (3–7) in children and adolescents, and approximates 35% in adults in the United States (8). The presence of metabolic syndrome is associated with an increased risk of the development and progression of cardiovascular disease and type II diabetes in both children (9–11) and adults (12–14). Recent studies that utilized continuous risk factor clustering scores show associations with obesity (15) and physical activity (16,17), which suggests that risk factor clustering may be modifiable by changes in lifestyle.

Since the prevalence of metabolic syndrome is increasing over time in both adolescents (18) and adults (19), it is important to understand its development and the extent to which cardiometabolic risk factor clustering is stable and/or predictive of adult clustering. Tracking refers to both the stability and predictive ability of a variable measured at different time points (20). Individual cardiovascular disease risk factors track by varying degrees from adolescence into adulthood (21); however, the magnitude of their stability varies among the risk factors: adiposity, total cholesterol and lipids appear to have better stability than blood pressure (21–25), glucose and triglycerides (26). Despite the varying strength of trends, abnormal levels of individual cardiometabolic risk factors show persistence from childhood into adulthood (21,26).

In addition to individual risk factors, evidence is accumulating that cardiometabolic risk factor clustering may also be a stable characteristic from childhood through adulthood. A recent American Heart Association scientific statement concluded that future research was needed to evaluate the stability of metabolic syndrome phenotypes over time in childhood and adolescents in large-scale,
Definitions of cardiometabolic risk factor clustering

It is important to describe and compare the definitions of cardiometabolic risk factor clustering used in the tracking literature. Definitions across studies differ in several respects, including 1) the specific cardiometabolic risk factors considered, 2) the thresholds and criteria for determining “abnormal” levels of the risk factor, and 3) the number of risk factors that determines “clustering” in a single individual. Most studies include a measure of blood lipids and blood pressure with a combination of other cardiometabolic risk factors, such as fasting blood glucose (24,28,29), insulin (28,30), or body composition (total body fat, body mass index, or waist circumference) (24,25,28,29,31). One study also included a behavioral risk factor (smoking) in the definition of clustering (25). Cardiometabolic risk factor clustering is usually defined using combinations of three (30,32) to six (24,25) risk factors. An alternative approach to studying risk factor clustering without using thresholds for a specific risk factor is to compute continuous risk factor scores, either by using principal components analysis (17,24), or by summing residuals or z-scores (15,16,29). The criteria to establish “high risk” cardiometabolic clustering varies across studies. Some studies assign each individual a cardiometabolic risk factor clustering “score” derived from the sum of sample-specific rankings (25,29,30), or a composite score derived from principal component analyses (24). Other techniques involve categorizing individuals into tertiles (32) or quartiles (28,31) of risk. Individuals in the highest or lowest (high density lipoprotein cholesterol [HDL-C]) category are classified as “high risk”. Studies that use this categorization to identify “high risk” may require that all cardiometabolic risk factors considered are in the “high risk” category (28,32), whereas others require that the majority of cardiometabolic risk factors assessed are “high risk” (31). These differences in defining risk factor clustering make it challenging to directly compare results across studies. Despite these challenges, cross-sectional analyses have shown that cardiometabolic risk factor clustering occurs in children and adolescents more often in boys than girls (4,33), preadolescent and young adults in comparison with adolescents (34), in Mexican-Americans and whites versus African-Americans (4,5,34), and in the overweight and obese more often than in those who are normal weight (4,5,34,35). The most common high risk phenotype reported was elevated triglycerides and low HDL-C; and the least common phenotype was fasting glucose (4,5).

Definition of tracking

Tracking is a term used to describe a variable’s longitudinal development involving both the stability (maintenance over time of ranking within a distribution) and predictability of future measures from earlier measures (20,36,37). At a minimum, measurements are required on the same individuals at two time points. In order to compare the strength of tracking between studies, it is important to consider the effects of initial age, periods in life, such as childhood, adolescence and young adulthood, biological maturation, length of the period between the measurements, as well as the methodology used to define tracking (20). Although only two time points are minimally required to assess tracking, some longitudinal studies may include multiple serial measurements. Common methods to assess tracking include growth curve models (36-38), inter-age correlation coefficients (24,25,29-31), maintenance of rank or relative position over time (within quartile, quintiles, etc) (25,28,30,32), proportion of subjects remaining above/below a predetermined cut-point (28), or calculation of intra-class correlations (ICC) (39). Analyses that evaluate change in rank using sample-specific quantiles to assess cardiometabolic clustering limits direct comparisons that can be made between studies (20).

Methods

A literature search was conducted using PubMed in order to search for articles, which assessed the tracking of cardiometabolic risk factor clustering from childhood to adulthood. Titles of articles and abstracts were examined for specific keyword combinations of cardiometabolic clustering and tracking. Other search terms used for the literature search included ‘stability’, ‘persistence’, ‘longitudinal’, ‘metabolic syndrome’, ‘syndrome X’ and ‘insulin resistance syndrome’. In addition to the computerized literature search, the reference lists of relevant papers were searched for other pertinent articles. If multiple articles were identified from the same cohort study, the most representative analysis was chosen based on
Results

A total of seven articles were identified that included both a childhood and adulthood assessment of cardiometabolic risk factor clustering and an analysis of its stability over time. Some articles identified in the search were excluded if they did not report a measure of cardiovascular risk factor clustering (n = 13), assessed short-term tracking in either the childhood period only (n = 4) and/or the adulthood period only (n = 3), were not an original investigation (n = 1), presented data from a cohort study already included in this review but in a specific subsample (n = 3), examined longitudinal development of clustering but without assessment of tracking (n = 3), or reported statistical techniques not considered equivalent to tracking (n = 1).

Table I summarizes the methods and results of the seven studies included in this review. Some of the reviewed studies determined clustering within a sample of adolescents (25,29,31) or in a sample of children and adolescents combined (24,28,30,32). Sample sizes varied from 48 (29) to 1 974 (32). The age at baseline varied among studies from 4–5 years (28,30) to 15–16 years (25,29,31). The length of follow-up also varied between 6 years (32) and 15.8 years (28). Despite these differences, studies consistently found that cardiometabolic risk factor clustering tracks from childhood and/or adolescence into adulthood. Several studies incorporated multiple statistical strategies, but for the purpose of this review, results will be grouped by statistical technique: inter-age correlations, percentiles/rankings and regression.

Inter-age correlations

The use of inter-age correlations is the most commonly employed method of assessing stability or tracking. Inter-age correlations (r) for the tracking of cardiometabolic risk factor cluster scores generally demonstrate a moderate level of tracking between childhood and/or adolescence into adulthood. Despite varying definitions of cardiometabolic clustering (see Table I for specific definitions), among the five studies that presented inter-age correlations, the values ranged from 0.42 in the Danish Youth and Sport Study (31) to 0.64 in the Bogalusa Heart Study (30). Reasons for variability in the results may be explained by true biological differences within and between individuals over time, or differences in the measurement error associated with the specific variables included in the risk factor clustering definition (20).

Bao et al. showed that a risk clustering score had a higher inter-age correlation (r = 0.64) than each of the individual risk factors (range: r = 0.34–0.57) in the Bogalusa Heart Study (30), although these were not statistically tested for differences. In contrast, Eisenmann et al. found comparable tracking correlations between individual cardiometabolic risk factors (ranges: r = 0.24–0.79) and a risk clustering score (r = 0.56) (29).

Katzmarzyk and colleagues also found comparable tracking of individual risk factors (range: r = 0.41–0.71) and a composite risk score (male: r = 0.51; females: r = 0.46) in the Quebec Family Study (24). Although the level of tracking was comparable between males and females in the Quebec Family Study, Andersen and colleagues found that risk factor clustering was more stable over time in Danish males (r = 0.67; p < 0.001) than in females (r = 0.33; NS) (25).

Rankings/High risk groups

Given that threshold levels of cardiometabolic risk factors are used to define the level of disease risk, the use of distributional or biological cut-offs are often used to rank individual risk factors and levels of clustering. A total of five studies included in Table I used a percentile or ranking approach to assess tracking. Andersen and Haroldsdottir found that 50% and 42% of Danish males and females, respectively, remained in the upper quintile of a risk factor cluster score over 8 years of follow-up (25), whereas a higher proportion (61%) of subjects remained in the upper quintile of risk over 8 years in the Bogalusa Heart Study (30). Finally, 25% of a “high risk” group, determined by partitioning risk factors into tertiles, also remained at adulthood over 6 years of follow-up.
## Table I. Summary of studies for cardiometabolic risk factor clustering tracking from childhood to adulthood.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study/Subjects</th>
<th>Baseline Age</th>
<th>Follow-up Period/Length</th>
<th>Definition of Risk Factor Clustering</th>
<th>Results</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td>Andersen &amp; Haraldsdottir (25)</td>
<td>Danish Males = 88, Females = 115</td>
<td>15-19 y</td>
<td>1983 to 1991, 8 y</td>
<td>Risk variables (skinfolds (BF), SBP, DBP, TC, HDL, TG, smoking) ranked 1–6 and scores were summed.</td>
<td>Inter-age correlations: Males: r = 0.67 (p &lt; 0.0001) Females: r = 0.33 (NS) Percent remaining in upper quintile: Males: 50% Females: 42%</td>
<td>Risk factor cluster scores were more stable over time in males than in females.</td>
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<td>Bao et al. (30)</td>
<td>Bogalusa Heart Study</td>
<td>White: Males = 327, Females = 337, Black: Males = 238, Females = 274</td>
<td>5–17 y</td>
<td>1981–82 to 1988–91, 8 y</td>
<td>Sum of sex-, race- and age-specific rankings of risk variables (SBP, TC:HDL, insulin).</td>
<td>Inter-age correlation: r = 0.64 p &lt; 0.0001 Percent remaining in upper quintile: 61%</td>
</tr>
<tr>
<td>Raitakari et al. (32)</td>
<td>Cardiovascular Risk in Young Finns Study</td>
<td>Males = 927, Females = 1047</td>
<td>6–18 y</td>
<td>1980 to 1986, 6 y</td>
<td>A high risk group was defined as being in the age- and sex-specific upper tertiles of TC and DBP and the lower tertile of HDL.</td>
<td>25.4% of those in the high risk group at baseline remained in the high risk group at follow-up (p = 0.002)</td>
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<td>Katzmarzyk et al. (24)</td>
<td>Quebec Family Study</td>
<td>Males = 76, Females = 71</td>
<td>8–18 y</td>
<td>1980 to 1992, 12 y</td>
<td>Composite risk score from principal components analysis of risk variables (skinfolds, HDL, MAP, TG, TC:HDL, glucose).</td>
<td>Partial inter-age correlations, adjusted for age and length of follow-up: Males: r = 0.51 Females: r = 0.46</td>
</tr>
<tr>
<td>Andersen et al. (31)</td>
<td>Danish Youth and Sport Study</td>
<td>Males = 133, Females = 172</td>
<td>16–19 y</td>
<td>1983 to 1991, 8 y</td>
<td>Risk factor clustering defined as 2+ risk variables in the upper quartile (TC:HDL, SBP, TG, BF).</td>
<td>Probability for clustering at follow-up from baseline: 6.0 (95% CI 2.1–16.9) Inter-age correlation for number of risk factors: r = 0.42 (p &lt; 0.0001)</td>
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in the Cardiovascular Risk in Young Finns Study (32). Results from the Danish Youth and Sport Study indicate that adolescents with two or more cardiometabolic risk factors in the upper quartile were six times more likely to also have cardiometabolic risk factor clustering as adults (31). Finally, Chen and colleagues have demonstrated that children in a low risk factor clustering group had a lower prevalence of risk factor clustering and NCEP-defined metabolic syndrome as adults compared with children with moderate and higher levels of risk factor clustering (39). The tracking of low risk from childhood to adulthood has important implications for early lifestyle and behavioral intervention in high-risk children in order to reduce cardiovascular risk and progression in adulthood.

**Influence of obesity**

Children who are overweight or obese in childhood have increased odds of having cardiovascular risk factor clustering in adolescence than their normal weight counterparts (31). Further, body fatness has been shown to be related to the development of a high-risk cardiometabolic profile in early adulthood (42) and also to the development of metabolic syndrome (33). The presence of obesity was also associated with a greater tracking magnitude of cardiovascular risk factor clustering from childhood/adolescence into adulthood in the Bogalusa Heart Study (30). For each SD higher body mass index (BMI) in childhood, the odds of having cardiovascular risk factor clustering as an adult was 2.03 (44). Increases in body fat over time also resulted in adverse effects on the individual cardiometabolic risk factors in the Amsterdam Growth and Health Study (45). An important consideration in cardiovascular risk factor tracking is an assessment of individuals (children and/or adolescents) who have developed a high-risk cardiometabolic profile in early adulthood (42) and also to the development of metabolic syndrome in childhood/adolescence with a greater tracking magnitude from childhood/adolescence into adulthood in the Bogalusa Heart Study (30).

### Table I. (Continued)

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<td>Eisenmann et al. (29)</td>
<td>Aerobics Center Longitudinal Study Males = 36 Females = 12</td>
<td>12-18 y</td>
<td>1970 to a subsequent visit where age &gt;21 y 10.9 y</td>
<td>Composite risk score computed by summing age- and gender-adjusted residuals for WC, HDL, TG, glucose and MAP. A low risk group was defined as being in the lower quartiles for three or more of age-, race- and sex-adjusted BMI, HOMA-IR, SBP, and TC:HDL.</td>
<td>Partial inter-age correlation, adjusted for age and length of follow-up: ( r = 0.56; p&lt;0.05 )</td>
<td>Tracking of the composite risk score was comparable with individual risk factors.</td>
</tr>
<tr>
<td>Chen et al. (28)</td>
<td>Bogalusa Heart Study White: Males = 399 Females = 523 Black: Males = 219 Females = 333</td>
<td>4-17 y</td>
<td>1982 to 2003 15.8 y</td>
<td>A low risk group was defined as being in the lower quartiles for three or more of age-, race- and sex-adjusted BMI, HOMA-IR, SBP, and TC:HDL.</td>
<td>Children in the low risk group had a lower prevalence of high risk factor clustering (3 + risk variables in upper quartile) as young adults: (3.8% vs. 14.6%; ( p&lt;0.001 ))</td>
<td>Results were similar for NCEP metabolic syndrome: (4.6% vs. 12.9%; ( p = 0.005 ))</td>
</tr>
</tbody>
</table>

**Abbreviations:** BF: body fat, BMI: body mass index, DBP: diastolic blood pressure, HDL: high density lipoprotein cholesterol, HOMA-IR: homeostasis model assessment of insulin resistance, MAP: mean arterial blood pressure, NCEP: National Cholesterol Education Program, SBP: systolic blood pressure, TC: total cholesterol, TC:HDL: total cholesterol to high density lipoprotein ratio, TG: triglycerides, WC: waist circumference, y: years.
risk factors tend to cluster together, and that obesity is an important determinant in the development of metabolic syndrome.

Future research directions and recommendations

The studies presented in this review all varied in terms of the risk factors considered, as well as the definition of high risk. Although standardized definitions of cardiometabolic clustering and metabolic syndrome have not been established in children or adults, utilizing continuous risk factor scores (15,16) or an established definition for metabolic syndrome (1,2,46–48) may provide better generalizability of the results to the general population as well as improving comparisons between studies. Furthermore, more robust statistical methodologies for serial data may be useful for analyzing future studies for cardiometabolic risk factor tracking (49,50).

Another consideration when interpreting tracking studies of cardiometabolic risk from childhood to adulthood is the age at initial measurement, as well as the age at follow-up. Interestingly, cardiometabolic risk factor clustering tracking indicates that high-risk children and adolescents have poor stability over the short-term. For instance, the stability of children and adolescents with two or more risk factors is 46% over a year, indicating that approximately 50% improve their cardiometabolic profile within a year’s time (22). Three year tracking within adolescents also shows low levels of cardiometabolic risk factor clustering tracking during the adolescence (33). This may suggest that cardiometabolic tracking varies over different periods of life within childhood and/or adolescence due to hormonal and maturational changes. Thus, the age at the initial time point for a tracking study between childhood and adulthood may affect the results. In addition, most existing longitudinal studies follow participants into their mid to late twenties, whereas few studies have followed subjects beyond early adulthood.

As fitness, physical activity and obesity are also closely related to cardiometabolic risk factor clustering (15–17), it will also be important for future studies to include these measures in their assessment of cardiometabolic risk and to determine their influence on the tracking of individual risk factors and risk factor clustering.

Future studies are needed to 1) clarify the short-term stability of cardiometabolic risk factor clustering during childhood and adolescence, 2) expand our understanding of long-term tracking from childhood beyond the third decade of life, 3) clarify the role of gender on estimates of stability, 4) expand our understanding of cardiometabolic risk factor clustering in different racial and ethnic groups, and 5) include the influence of lifestyle behaviors associated with cardiometabolic risk factor clustering, such as fitness and physical activity, in tracking analyses.

Summary and conclusions

Although a limited number of articles were identified for this review according to the inclusion criteria, the weighted evidence supports that cardiometabolic risk factor clustering tracks between childhood and adulthood. Despite varying definitions of “high risk” within childhood, as well as methodologies to assess tracking between childhood and adulthood, the results show that cardiometabolic risk factor clustering is generally stable between childhood and adulthood, and that in general, clustering scores track at least as well as individual cardiovascular disease risk factors. However, a substantial portion of the variability in stability remains unexplained, which highlights the phenotypic plasticity of these metabolic characteristics. Some gaps in the literature exist concerning gender and race effects, which future research should attempt to clarify.

These findings have important implications for the prevention of cardiovascular disease. As cardiometabolic clustering is stable and predictive of adult status, early behavioral and lifestyle interventions for high-risk children and adolescents may be beneficial to decrease overall cardiovascular risk and prevent the progression of cardiovascular disease in adulthood.

Conflict of interest

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Declaration of interest: The authors alone are responsible for the content and writing of the paper.

References


Tracking of cardiometabolic clustering