

**Lifestyle Interventions to Change Trajectories of Obesity-Related Cardiovascular Risk from Childhood Onset to Manifestation in Adulthood**

A joint Scientific Statement of the Task Force for Childhood Health of the European Association of Preventive Cardiology (EAPC) and the European Childhood Obesity Group (ECOG).

Short title: Childhood Cardiovascular Risk Trajectories

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20 **Total word count:** 5870

21 **Abstract word count:** 202

22 **Key words:** childhood obesity, prevention, cardiovascular risk trajectories, lifestyle

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1 **Abstract**

2 There is an immediate need to optimize cardiovascular (CV) risk management and primary  
3 prevention of childhood obesity to timely and more effectively combat the health hazard and  
4 socioeconomic burden of CV disease from childhood development to adulthood manifestation.  
5 Optimizing screening programs and risk management strategies for obesity-related CV risk in  
6 childhood has high potential to change disease trajectories into adulthood. Building on a  
7 holistic view on the etiology of childhood obesity, this document reviews current concepts in  
8 primary prevention and risk management strategies by lifestyle interventions. As an additional  
9 objective, this scientific statement addresses the high potential for reversibility of CV risk in  
10 childhood and comments on the use of modern surrogate markers beyond monitoring weight  
11 and body composition. This scientific statement also highlights the clinical importance of  
12 quantifying CV risk trajectories and discusses the remaining research gaps and challenges to  
13 better promote childhood health in a population-based approach. Finally, this document  
14 provides an overview on the lessons to be learned from the presented evidence and identifies  
15 key barriers to be targeted by researchers, clinicians and policymakers to put into practice  
16 more effective primary prevention strategies for childhood obesity early in life to combat the  
17 burden of CV disease later in life.

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## 1 **1. Introduction**

2 Obesity is currently one of the most serious global public health problems. There is robust  
3 evidence that metabolic and cardiovascular (CV) risk factors and psychosocial complications  
4 are already present in children with obesity and worsen in adulthood.<sup>1-5</sup> Childhood obesity is  
5 commonly defined as BMI > 95th percentile for age and sex in children older than 2 years of  
6 age.<sup>6</sup> Between 1980 and 2013, the worldwide prevalence of childhood obesity increased by  
7 47%.<sup>7</sup> The WHO European Childhood Obesity Surveillance Program (COSI) revealed that  
8 overweight and obesity rates among primary school children range from 15–52% in boys and  
9 from 13–43% in girls, with higher prevalence in southern European countries.<sup>8</sup> The lifetime  
10 costs of a child or adolescent with obesity have previously been estimated to be about € 150  
11 000 for both sexes.<sup>9</sup>

12 Obesity is associated with an increase in CV risk factors in children.<sup>10,11</sup> The rise in childhood  
13 obesity has subsequently been linked to an increase in non-communicable diseases such as  
14 type 2 diabetes mellitus (T2DM),<sup>12</sup> hypertension<sup>10</sup> and atherosclerosis as target organ damage  
15 in young men.<sup>13</sup> A body of evidence exists on obesity-related CV risk in childhood, for example,  
16 higher systolic blood pressure (BP) in children with overweight (+4.5 mmHg) and obesity (+7.5  
17 mmHg), with signs of adverse concentrations of blood lipids and higher left ventricular mass  
18 compared to normal weight children.<sup>10</sup> The number of risk factors increases with severity of  
19 childhood obesity.<sup>11</sup> The high prevalence of childhood obesity is worrying at the individual as  
20 well as public health level, as it has been linked with CV morbidity and mortality in  
21 adulthood.<sup>3,14,15</sup> Because of the persistent high prevalence rates and the risk trajectories into  
22 adulthood, it is important to reduce CV risk as early as childhood. As key determinants,  
23 childhood physical inactivity and unhealthy diet contribute to the development of obesity-  
24 related CV risk, and thus to the development of non-communicable diseases later in life.

25 In this document, we briefly review the etiology of childhood obesity and current approaches  
26 for its management. The novel focus lies on the discussion of obesity-related risk trajectories  
27 from childhood to adulthood and on the need for childhood screening programs and  
28 consecutive preventive strategies. As a main aim, both physical activity (PA) and exercise as  
29 well as nutrition behavior and diet are extensively reviewed as key risk managing strategies.  
30 This scientific statement does not intend to systematically review previous meta-analyses or  
31 international guidelines on the management of childhood obesity. Rather, it aims at giving  
32 expert insights on how obesity-related childhood CV risk may need to be approached in order  
33 to change risk trajectories as primary prevention strategies to reduce the high burden of CV  
34 disease.

## 35 **2. Etiology and management of obesity-related CV risk in childhood**

### 36 **Beyond caloric imbalance – the environment and biological factors**

1 Obesity-related CV risk is caused by a complex interplay between genetic factors and the  
2 environment (**Figure 1**). Individual genetic predisposition, epigenetics, endocrine, metabolic  
3 and immunologic responses interact with the child's nutrition, PA, sleep habits and  
4 psychological factors.<sup>16</sup> Later in life, an association of genetic susceptibility and healthy lifestyle  
5 with incidence coronary artery disease and stroke has been shown in patients with  
6 hypertension.<sup>17</sup>

7 During early gestation, maternal diet and environmental factors can, for example, modify  
8 methylation status and thereby gene expression.<sup>18</sup> Even before conception, both maternal and  
9 paternal health and lifestyle behaviour affect the epigenetic phenotype of the offspring with  
10 potential consequences for the gestational development.<sup>19,20</sup> Moreover, psychological factors  
11 and the interaction between gut and brain hormones influence satiety mechanisms.<sup>21</sup> The gut  
12 microbiota and exposure to toxins and viruses contribute to the development of obesity. In  
13 addition, so-called industrially produced endocrine-disrupting chemicals appear to be  
14 obesogenic.<sup>22</sup> Thus, the underlying mechanisms for the development of obesity in childhood  
15 are complex and need to be accounted for in future obesity prevention policies. Importantly,  
16 medical history needs to be considered and plays an important role in the detection of other  
17 causes of obesity, such as hormonal disturbances or specific antipsychotic medication.

### 18 **Role of parents, socioeconomic status and education**

19 The role of family, caregivers, and peers in the development and maintenance of obesity in  
20 children is crucial. Several complex biological and social interactions between parent and child  
21 need to be considered. Maternal body mass index (BMI) at conception strongly predicts  
22 offspring BMI throughout childhood.<sup>23</sup> Prenatal maternal lifestyle, parenting style, feeding  
23 habits in early childhood and family nutrition habits are important factors to help foster a healthy  
24 lifestyle and promote awareness of internal hunger and satiety cues.<sup>24</sup> Breast-feeding may also  
25 play a central role for obesity risk reduction, interacting with psychosocial and environmental  
26 factors.<sup>25, 26</sup> Maintenance of a healthier diet was achieved in studies that specifically targeted  
27 parenting, modification of home environment and behavioral constructs.<sup>27</sup>

28 Unhealthy food habits and low PA levels, as assessed by sedentary behaviors such as screen  
29 time, have been associated with low familial socio-economic status and varying quality of child  
30 care.<sup>28-30</sup> Maternal, and not paternal, psychiatric symptoms have been shown to be associated  
31 with the severity of obesity in their offspring.<sup>31</sup> Implementing healthy lifestyle in the education  
32 of children is challenged by an irritable or reactive temper in children with overweight and  
33 obesity, which may be accompanied by anxious feelings, depressed mood, psychosomatic  
34 complaints or impulsive behavior, aggression, oppositional behavior.<sup>32</sup>

### 35 **Media (mis-)use, role models, psychological aspects**

1 Unhealthy food marketing in media and social media is a powerful determinant of unhealthy  
2 diets and obesity among children and adolescents.<sup>33</sup> Foods embedded in entertainment media  
3 affect food choices and food intake in children. In addition to high caloric value most of the  
4 embedded foods have low nutritional values. Most children are exposed to promotion and  
5 marketing of products such as fast food and sugar-sweetened beverages up to about 200  
6 times per week on social media.<sup>34</sup> Of note, social media influencer marketing of unhealthy  
7 foods increased children's immediate food intake, whereas the equivalent marketing of healthy  
8 foods had no effect.<sup>35</sup> Therefore, promotion of healthy foods on social media may not be an  
9 effective means to improve healthy dietary behaviors in children. An association of fast-food  
10 consumption with adverse blood lipids and vascular impairments has been shown in adults but  
11 to a much lesser extent in children, indicating the opportunity for primary prevention in  
12 childhood.<sup>36</sup>

13 Beyond PA and nutrition, psychological aspects are often associated with health status of  
14 children with obesity and should be addressed in prevention and lifestyle interventions.  
15 Individuals with obesity often experience social stigma in multiple settings, including the  
16 medical community.<sup>37</sup> Such stigmata may lead to serious physical and psychological  
17 consequences (for example, promoting obesity, eating disorders, stress and depression, and  
18 barriers to PA) and less frequent use of adequate medical care. Addressing weight stigma is  
19 therefore important to improve health and well-being in children with obesity.<sup>38</sup>

## 20 **Management: What the guidelines say**

21 Clinical guidelines recommend that lifestyle changes should be the initial step for the  
22 management of obesity and CV risk factors in children.<sup>6</sup> An overview of the classic  
23 cardiometabolic risk factors associated with childhood obesity and their definitions are shown  
24 in **Table 1**. Recommended targets for PA levels for school-age youth have been defined as  $\geq$   
25 60 min/day of moderate to vigorous aerobic PA (MVPA). In addition, muscle strengthening and  
26 activities that increase bone strain are to be implemented at least 3 times per week. The time  
27 being sedentary, particularly the amount of screen time, should be limited.<sup>39, 40</sup> With respect to  
28 diet, the guidelines recommended that children consume  $\leq$  25 g (100 kcal or  $\approx$  6 teaspoons) of  
29 added sugars per day.<sup>41</sup> Few children achieve such low levels, making this an important public  
30 health target. With respect to sodium intake, the WHO has recommended that children aged 2  
31 to 15 years should reduce their intake to better control BP. Based on the estimated energy  
32 requirements of children compared with adults, the recommended adult sodium intake of a  
33 maximum level of 2g sodium (5g salt) per day should be adjusted downward.<sup>42</sup> According to  
34 the United Nations Children's Fund,<sup>43</sup> main other dietary advice are: eat an adequate  
35 breakfast, avoid eating between meals, eat three meals and no more than two snacks per day,  
36 limit portion sizes, avoid energy-dense and nutrient-poor foods (for example, fruit juices or fast

1 food), increase intake of unprocessed fruit, vegetables and fibre-rich cereals. Also, lowering  
2 fat and sugar intake should be main targets.<sup>44,45</sup>

3 Early implementation of family-based multicomponent behavioral interventions with a minimum  
4 of 26 contact hours for children and adolescents with overweight and obesity aged 2 to 18  
5 years is recommended.<sup>46</sup> However, there is insufficient evidence to recommend specific forms  
6 of interventions with respect to comparative effectiveness in patients and families with different  
7 socioeconomic backgrounds.<sup>46</sup> Recommendations for patient care and frequency of risk factor  
8 monitoring in children with established CV risk such as hypertension, T2DM and dyslipidemia,  
9 have been expressed in previous international guidelines.<sup>6,46-48</sup>

10 The American Academy of Pediatrics has proposed different treatment strategies dependent  
11 upon the severity of obesity. This includes treatment for children or adolescent with overweight  
12 or obesity that can be delivered in primary care or a community-based setting, and intensive  
13 multicomponent interventions, pharmacotherapy and/or bariatric surgery delivered to  
14 adolescent with obesity or severe obesity in secondary or tertiary settings.<sup>49, 26</sup> For severe  
15 obesity and T2DM in children over the age of 10, metformin has been shown to be beneficial  
16 for the treatment of insulin resistance and to support weight loss.<sup>50</sup> Orlistat (FDA approval) and  
17 liraglutide (EMA approval) may also be considered as adjunct treatment in addition to lifestyle  
18 modifications in children with obesity older than 12 years.<sup>6,51</sup> For adolescents with a BMI  
19 greater than 35 kg/m<sup>2</sup>, bariatric surgery in combination with lifestyle modifications may be  
20 considered,<sup>6</sup> but there are no data from randomized controlled clinical trials (RCTs) on the  
21 effectiveness of bariatric surgery in this age group.<sup>52</sup> A RCT comparing bariatric surgery to  
22 combined lifestyle interventions in adolescents is still ongoing.<sup>53</sup>

### 23 **3. Risk trajectories from childhood to adulthood**

24 The impact of CV risk factors such as obesity and hypertension on the development of CV  
25 disease and outcome are well understood in the adult population. These causal factors for an  
26 increased CV disease risk are already present in children and adolescents and are key  
27 determinants of adult health. A recent systematic review which included more than 100 000  
28 individuals reported that children with excess weight had higher risk for T2DM, hypertension  
29 and dyslipidaemia as an adult.<sup>54</sup> Decreasing physical activity (PA) and persistent inactivity  
30 have been shown to predict adult obesity and associated CV risk profiles.<sup>55,56</sup>

31 Children with obesity are five times more likely to suffer from obesity as adults compared to  
32 those without childhood obesity.<sup>57</sup> Childhood overweight and obesity are associated with a  
33 concomitant increased prevalence of elevated and high BP. The longitudinal Cardiovascular  
34 Risk in Young Finns Study showed that elevated BP in childhood tracks into adulthood.<sup>58</sup>  
35 Moreover, systolic BP in late adolescence was an independent predictor for coronary heart  
36 disease (CHD) in mid-adulthood.<sup>59</sup> In a study of 2.3 million adolescents, obesity during



1 adolescence was associated with a substantially increased CV mortality in middle age.<sup>60</sup> A  
2 large cohort study in children demonstrated the association of a higher childhood BMI with an  
3 increased risk of CHD in adulthood.<sup>61</sup> A limitation of these studies is their retrospective design.  
4 Nonetheless, the increased obesity rate in adolescence is thought to lead to an estimated 5-  
5 16% increase in incidence CHD in 2035.<sup>62</sup> In a recent prospective cohort study from the  
6 International Childhood Cardiovascular Cohort (i3C) Consortium, childhood risk factors were  
7 shown to be associated with CV events in midlife.<sup>1</sup>

8 To reduce the obesity-induced accelerated CV disease risk in children, preventive  
9 interventions are essential. A meta-analysis which assessed a total of 85 RCTs reported that  
10 lifestyle interventions positively influenced BMI as well as systolic and diastolic BP.<sup>63</sup> Lifestyle  
11 interventions based on PA and nutrition in children<sup>64,65</sup> and adolescents<sup>66</sup> with overweight and  
12 obesity have previously been explored. Multicomponent behaviour-changing interventions  
13 seemed to have beneficial, albeit small effects on weight reduction in children of all age groups  
14 with low rates of adverse events.<sup>67</sup> Of note, mainly weight-related measures have previously  
15 been reported while information on overall health, cardiometabolic and psychological factors  
16 are so far limited. Thus, PA and exercise as well as nutrition behaviour and diet are reviewed  
17 in this document with updated findings as potential risk managing strategies during childhood.  
18 Overall, weight loss treatment and reduction of associated overall CV risk for children and  
19 adolescents need to be better investigated and long-term follow-up studies are necessary to  
20 better quantify and improve the health trajectory for the next generation. The principal concept  
21 and potential impact of a multi-modal screening program in childhood to reduce cumulative  
22 lifetime CV risk is visualized in **Figure 2**. The implementation of screening programs for  
23 obesity-related CV risk is discussed in the next chapter.

24 For children and adolescents, the consequences of the COVID-19 pandemic with lockdowns  
25 and closures of schools and sports clubs are threatening their long-term health. A review with  
26 more than 17 000 000 children, adolescents and young adults concluded that lockdowns  
27 resulted in increased weight gain and adversely impacted food choices.<sup>68</sup> Physical inactivity,  
28 even before the COVID pandemic, has become a major attributable factor associated with  
29 development of childhood obesity and related CV risk factors.

#### 30 **4. Screening programs for obesity-related cardiovascular risk and surrogate markers**

31 In childhood, the obesity-related predisposition for atherosclerosis can be non-invasively  
32 assessed by use of structural and functional vascular biomarkers that allow for diagnosis of  
33 subclinical atherosclerosis as cumulative surrogates for overall CV risk.<sup>69</sup> Childhood obesity is  
34 associated with endothelial dysfunction, irrespective of pubertal stage, even in the absence of  
35 comorbidities. Lifestyle interventions have the potential to reverse adverse vascular  
36 alterations. In children, a high reversibility of adverse CV risk was found after intensive lifestyle

1 interventions including diet alone, exercise alone or a combination of both.<sup>70</sup> Improvements  
2 were reported for body composition, metabolic parameters, brachial artery flow-mediated  
3 dilatation (FMD) and carotid intima-media thickness (cIMT).<sup>70</sup> Retinal arteriolar narrowing, an  
4 established microvascular biomarker of CV risk in adults, has recently been shown to predict  
5 development of high BP in 6-8 year old children after a 4 year follow-up.<sup>71</sup> Increases in  
6 cardiorespiratory fitness (CRF) were associated with reduction in BMI and consequently wider  
7 retinal arterioles at follow-up.<sup>71</sup> Use of time-efficient, affordable, non-invasive biomarkers of  
8 vascular health represents a promising perspective for the screening of cumulative CV risk in  
9 children once resilient normative data throughout childhood and adolescence have been  
10 established. In adolescent boys and girls, CRF with a maximum oxygen uptake of below 42  
11 and 35 mL/kg/min respectively, was associated with a 5.7- and 3.6 -times greater likelihood of  
12 having CV disease risk later in life.<sup>72</sup> A reduced maximal oxygen uptake per lean body mass  
13 and reduced peak cycling power output are common in children and adolescents with obesity  
14 and underline the importance for the assessment of CRF in childhood screening programs and  
15 for the prescription of exercise-based prevention programs.<sup>73</sup>

16 BMI has been most commonly measured in previous decades as it is easily applied and most  
17 practical. Thus, a vast amount of data is available on childhood BMI percentiles and z-scores.  
18 The additional benefits of using other measures of body composition, such as waist  
19 circumference (WC), for routine paediatric care in addition to BMI for predicting metabolic risk  
20 have been shown to be small.<sup>74</sup> The use of waist-to-height ratio has not been shown to be  
21 superior to BMI or WC in predicting CV risk related to childhood obesity.<sup>74</sup> In large-scale cohort  
22 studies, BMI thus remains the most commonly used measure. Screening for clusters of CV  
23 risk factors is a challenging task in pediatric populations with difficulties in defining clear  
24 thresholds. Changing body size and weight, age-related variations in BP and lipids, as well as  
25 differences in sex and race have led to clustering of various CV risk factors as continuous  
26 variables rather than using strict cutoffs, which has been shown to be beneficial for childhood  
27 risk management.<sup>75</sup> Screening programs should focus on CV risk beyond BMI to avoid  
28 stigmatization. In addition, other variables such as family history, early life insults including  
29 maternal gestational diabetes exposure, as well as socio-economic status, media  
30 consumption, smoking, alcohol consumption and drug abuse contribute to alterations in CV  
31 risk and should be accounted for in childhood and adolescence screening programs.

32 In adults, a nationwide screening program on obesity was associated only with small  
33 improvements in obesity and cardiovascular risk factors.<sup>76</sup> From a public health perspective,  
34 feasibility and long-term cost-effectiveness of childhood screening programs and interventions  
35 strategies at population level are to be established and remain challenging. A leadership role  
36 for school-based screening programs has been suggested and remains one of the most  
37 promising primary prevention strategies in a population-based approach. Nonetheless,

1 measures of primordial prevention need to go beyond school-based screening programs and  
2 should address transport to schools and school sports as well as after-school programs and  
3 school-community linkages including participation of family and friends to promote the  
4 implementation of a healthy lifestyle. Support is warranted from pediatricians, family doctors  
5 and health care workers as well as politicians and other stakeholders. However, the benefits  
6 and pitfalls, even potential harms (for example due to stigmatization) of screening programs  
7 for children with overweight and obesity remain to be elucidated.<sup>77</sup> While the necessity for the  
8 prevention and treatment of obesity-related CV risk in children are not debatable, clear  
9 recommendations on how to implement cost-effective screening programs for obesity-related  
10 risk factors such as childhood hypertension and dyslipidemia are still missing.<sup>78,79</sup>

11 Whether or not population-based screening programs have the potential to counteract the  
12 growing burden of obesity-related CV risk in childhood remains a matter of debate. Who, when  
13 and how to screen in order to identify those at increased risk and greatest need for support  
14 remain critical questions. To this respect, cost-effectiveness will remain critical. Screening  
15 programs with a leadership role of schools, together with family- and community-based  
16 support, can be the backbone for effective prevention strategies for almost all children,  
17 independent of their socioeconomic background.

## 18 **5. Physical activity and exercise as risk managing strategies**

19 In this chapter, we give an overview on the evidence for exercise interventions to reduce  
20 obesity-related CV risk as a risk managing strategy including systematic reviews and meta-  
21 analyses as well as RCTs. While we appraised each endpoint individually, we used  
22 standardised mean differences (SMD) as a useful tool to summarise effect estimates (with  
23 SMD around 0.2 considered small, SMD around 0.5 medium, and SMD around or above 0.8  
24 large).<sup>80</sup>

### 25 **Supervised exercise interventions**

26 A systematic review of meta-analyses on the effects of exercise-based interventions alone on  
27 health outcomes in children and adolescents with overweight or obesity showed consistent  
28 improvements in anthropometric and cardiometabolic outcomes.<sup>81</sup> Specifically, exercise  
29 interventions reduced body mass, BMI, fat mass, and central obesity, with overall small point  
30 estimates of effect for SMDs. These improvements were largely independent of duration of the  
31 sessions and exercise frequency, but programs cumulatively lasting a total of 1500 min or  
32 more were most effective in reducing BMI (either in absolute terms or as z-score), fat mass  
33 (%), visceral and subcutaneous fat. The pooled SMDs were small for some cardiometabolic  
34 outcomes (CRF, and fasting concentrations of circulating triglycerides and insulin), and  
35 medium for fasting glucose concentrations, whereas there was no significant overall effect of  
36 exercise on concentrations of total cholesterol, low density lipoprotein cholesterol (LDL-C), or

1 high density lipoprotein cholesterol (HDL-C).<sup>81</sup> In general, aerobic exercise training seemed to  
2 promote more beneficial changes in cardiometabolic parameters, and programs with higher  
3 intensities or volume yielded greater effects. Interventions of supervised exercise in children  
4 and/or adolescents (6-18 years old) with overweight and obesity induced significant reductions  
5 in cIMT, with a SMD of -0.31.<sup>82</sup>

6 A systematic review and network meta-analysis of randomised exercise interventions including  
7 aerobic exercise, combined aerobic and resistance exercise, as well as resistance exercise for  
8 4 weeks or more showed that the combination of aerobic and resistance exercise was most  
9 effective in reducing BMI z-scores among children with overweight and obesity, with a 32%  
10 improvement.<sup>83</sup> Aerobic exercise alone led to a 29% improvement in BMI percentiles, with no  
11 significant effect of resistance training alone. Another meta-analysis on the effect of aerobic,  
12 resistance, and combined exercise training on insulin resistance markers showed that training  
13 in general did not induce significant reductions in fasting plasma glucose but that aerobic  
14 exercise interventions reduced fasting insulin concentrations.<sup>84</sup> Aerobic exercise at vigorous  
15 or moderate-to-vigorous intensities in sessions of at least 60 min showed a superior effect than  
16 lower doses of exercise. High intensity interval training (HIIT) seems to elicit even greater  
17 improvements in CRF and reductions in systolic BP compared with other forms of aerobic  
18 exercise, but with no superior effects on body composition, circulating lipids, and diastolic BP.<sup>85</sup>

19 A later meta-analysis, which also included RCTs, however, concluded that there is insufficient  
20 evidence to determine if HIIT is more effective than traditional continuous endurance training  
21 with moderate intensity.<sup>86</sup> In the future, exergaming strategies may be used to guide children  
22 and adolescents to engage in more PA and exercise. A previous systematic review examined  
23 the potential role of exergames in improving weight status among overweight and obese  
24 children and adolescents.<sup>87</sup> There may be positive effects of active video games on weight-  
25 related outcomes in obese children and adolescents. However, available studies are limited in  
26 number and diversity. More research and high-quality studies are warranted to further explore  
27 the potential of exergaming in children and youth.

## 28 **Exercise interventions combined with other lifestyle interventions**

29 A meta-analysis on the efficacy of exercise interventions, alone or combined with other lifestyle  
30 interventions in adolescents (aged 10-19 years) with BMI  $\geq 85^{\text{th}}$  percentile, showed  
31 improvements in CRF, BMI, body mass, total lean mass, body fat percentage, systolic BP,  
32 insulin resistance, and glycaemic responses to an oral glucose tolerance test.<sup>88</sup> The SMD for  
33 these outcomes ranged from trivial (total lean mass: 0.10) to large (CRF: 1.27). There was  
34 inconclusive evidence for effects of exercise interventions on total cholesterol, LDL-C, HDL-C,  
35 fasting insulin or fasting blood glucose concentrations. Interventions with exercise, or advice  
36 on PA and/or diet, reduced hepatic fat content among adolescents (aged 14-16 years) with  
37 obesity, with an absolute reduction of 2%, which corresponded to a relative reduction of more

1 than 50% of existing hepatic fat.<sup>89</sup> Multicomponent lifestyle interventions that included  
2 supervised exercise training also reduced the prevalence of non-alcoholic fatty liver disease  
3 (NAFLD) after the intervention, with a pooled odds ratio of changes in NAFLD prevalence of  
4 0.38.<sup>90</sup> Supervised exercise-only or combinations of exercise and diet interventions reduced  
5 visceral adipose tissue (VAT) in youth (aged 7-19 years) with obesity.<sup>91</sup> Studies focusing on  
6 only exercise had the greatest effect (SMD=-0.85), while interventions combining exercise and  
7 diet showed a pooled SMD of -0.69. Yet, there were few high-quality RCTs on diet-only  
8 interventions and the studies to date showed a small effect (SMD=-0.23).

9 An umbrella review of meta-analyses on prevention and treatment of childhood obesity  
10 suggested that lifestyle interventions demonstrated small and short-term effects or no effect  
11 on body mass, and that parental involvement and reducing television time provided the  
12 greatest benefits in reducing obesity-related CV risk.<sup>92</sup>

### 13 **School-based interventions**

14 School-based interventions hold promise as a universal context to access and influence all  
15 children. However, the evidence for effectiveness of school-based interventions on CV disease  
16 risk factors is inconclusive. A systematic review and meta-analysis of 33 health education  
17 interventions aiming to reduce BMI in adolescents reported a statistically significant, albeit  
18 small effect of the interventions on BMI z-score (-0.06, 95% confidence interval [CI], -0.1 to -  
19 0.03,  $p < 0.001$ ).<sup>93</sup> Similar effectiveness of school-based interventions on change in BMI and  
20 BMI z-score were reported among primary school children.<sup>63</sup> Studies that showed significant  
21 effect on BMI outcomes among adolescents typically included a face-to-face component for  
22 intervention delivery in the classroom and lasted more than 12 weeks.<sup>93</sup> Furthermore, parental  
23 involvement accentuated the beneficial effect of interventions.<sup>63</sup> School-based PA programs  
24 that involved additional PA time produced small, yet significant reductions in waist  
25 circumference, diastolic BP, and circulating insulin levels among children aged 3-12 years, but  
26 with no overall effect on circulating HDL-C, LDL-C, triglycerides, and total cholesterol  
27 concentrations, or systolic BP.<sup>94</sup> Reductions in both diastolic and systolic BP were, however,  
28 reported after school-based lifestyle interventions.<sup>63</sup> Finally, the evidence is equivocal for  
29 effectiveness of school-based interventions for increased PA and reduced sedentary  
30 behaviour, with some meta-analyses reporting small, but significant effects on MVPA but not  
31 on sedentary behaviour<sup>95</sup>, and others reporting no effect of interventions on MVPA<sup>96</sup> or  
32 sedentary behaviour.<sup>97</sup>

### 33 **6. Nutrition behaviour and diet as risk managing strategies**

34 Landmark publications and meta-analyses on prevention and treatment of children and  
35 adolescents with overweight and obesity indicate that weight control may be obtained by a  
36 multicomponent intervention focused on life-long changes in dietary and PA behaviour.<sup>89,98,99</sup>

1 Healthy nutrition can, for example, act as a positive epigenetic factor during the critical  
2 developmental periods with impact on outcomes in adulthood. Therefore, nutritional  
3 interventions in children with overweight or obesity, standalone or in conjunction with exercise  
4 interventions, are first-line treatment options to reduce overall CV risk in young  
5 individuals.<sup>100,101</sup>

## 6 **Supervised nutritional interventions**

7 The diet effect on children with overweight and obesity has been evaluated using the BMI-SDS  
8 (Body Mass Index - Standard Deviation Score): a reduction >0.5 in a growing child correlated  
9 with better body composition and decreased CHD risk later in life.<sup>102</sup> In the 6-year post-  
10 intervention follow-up of the Special Turku Coronary Risk Factor Intervention Project (STRIP),  
11 beneficial effects of infancy onset dietary counselling on diet quality and cardiometabolic risk  
12 factors were found to be maintained into early adulthood.<sup>103</sup>

13 Prevention of adult CHD through interventions in childhood is supported by the fact that dietary  
14 habits and food preferences are formed early in life and that family-related lifestyle and eating  
15 habits tend to be maintained throughout the life span.<sup>104</sup> Several studies reported that the  
16 prescription of a low caloric diet is not effective in the medium-and long-term management of  
17 obesity among children, being associated to relapses and failures, increased risk of dropout  
18 and progression of obesity.<sup>105</sup> Implementation of a more intensive lifestyle intervention program  
19 with low carbohydrate- and low fat-diets has previously resulted in limited improvements in  
20 body composition and metabolic health.<sup>106</sup> The evidence regarding the impact of dietary  
21 interventions on obesity-related risk factors such as dyslipidaemia, hypertension, fasting  
22 hyperglycaemia and insulin resistance is inconclusive, according to a more recent systematic  
23 review of RCTs.<sup>107</sup> Also, a high protein diet did not improve anthropometric measures or other  
24 CV risk factors among children with overweight and obesity.<sup>108,109</sup> After a weight loss program  
25 including moderate energy-restricted diet and nutritional education, decreased oxidized LDL-  
26 C levels were found in children with the greatest weight loss (high-responders) and these levels  
27 were associated with improved BMI-SDS and cholesterol levels.<sup>110</sup> More research is needed  
28 to quantify achievable treatment targets by nutritional interventions to reduce CV risk in  
29 children with obesity.

## 30 **Nutraceuticals**

31 Alimentary fibres such as psyllium, glucomannan, guar gum and oats, have been shown to  
32 lower total cholesterol and LDL-C levels in children and adolescents.<sup>111,112</sup> For example, the  
33 use of phytosterol [1–2 g/day] can reduce total cholesterol levels in children with mild  
34 hypercholesterolaemia and in children with familial hyperlipemia,<sup>113</sup> but the long-term efficacy  
35 has previously been questioned in adults.<sup>114</sup> Other nutraceuticals, combined with dietary  
36 approaches, including red yeast rice,<sup>115</sup> omega-3 and omega-6 long chain polyunsaturated

1 fatty acids,<sup>116</sup> soy proteins<sup>117</sup> and probiotics, have been tested in children with  
2 hypercholesterolaemia.<sup>118</sup> A three-month treatment with alpha-lipoic acid and showed  
3 improvement of endothelial function and metabolic risk factors in youth with overweight or  
4 obesity.<sup>119</sup> Red yeast rice can lower LDL-C levels by inhibiting hepatic cholesterol  
5 metabolism.<sup>115</sup> Omega-3 long chain polyunsaturated fatty acids, in particular docosahexaenoic  
6 acid, act by improving quantitative levels of HDL-C and reducing triglycerides levels.<sup>116</sup> Soy  
7 protein has been shown to have lipid lowering effects. Blockage of bile acid and/or cholesterol  
8 absorption are possible mechanism underlying this effect, as well as the stimulation of the LDL  
9 receptor.<sup>117</sup> Probiotics may reduce blood cholesterol levels by several mechanism, including  
10 production of short-chain fatty acids that can interfere with cholesterol biosynthesis and an  
11 increase in bile acids excretion.<sup>118</sup>

## 12 **School-based interventions**

13 Several school-based lifestyle interventions showed good results for improving dietary habits  
14 in children and adolescent.<sup>63,120</sup> However, some studies found low-certainty evidence that  
15 reduced availability of sugar-sweetened beverages in schools is associated with decreased  
16 sugar-sweetened beverages consumption.<sup>121</sup> They found very low-certainty evidence for  
17 improved availability of drinking water in schools and school fruit programs being associated  
18 with decreased consumption of high caloric beverages. Reported associations between  
19 improved availability of drinking water in schools and student body weight varied.<sup>121</sup> In a  
20 previous RCT including 12 secondary schools including more than 600 pupils, it was found  
21 that the intervention, with a focus on nutrition education and improvement of the food  
22 environment, significantly lowered sugar intake but had no effect on fibre intake and fruit and  
23 vegetable consumption unless the quality of school lunches was improved.<sup>122</sup> Marketing for  
24 unhealthy food and beverage should be minimized or altogether prohibited, especially in  
25 schools, since it has been shown to negatively influence dietary preference in children.<sup>123</sup>  
26 Educational programs in schools may help fight the potentially negative influence of  
27 commercials and media models oriented to attract children towards high caloric foods and  
28 sedentary lifestyle.

## 29 **7. Research gaps and future needs**

30 Despite significant research advances into the physical, social, and economic consequences  
31 of childhood obesity in the last decades, there remain major research gaps in the peer-  
32 reviewed literature, as well as major challenges in the practical implementation of prevention  
33 and treatment strategies. The challenges and “lessons to be learned” can perhaps be  
34 summarized in these four key general areas: **1)** a need for further longitudinal research and  
35 RCTs, including comprehensive individual-level pooled analyses of existing large, high quality  
36 longitudinal studies; **2)** pushing for adoption of targeted clinical and social interventions; **3)**

1 emphasis on improved awareness among the healthcare sector, educational institutions,  
2 government, and general public; **4)** a need for changes in national and global policies to better  
3 mitigate the increasing risk trajectories of childhood obesity and their associated pressures on  
4 the healthcare system and society; and **5)** consideration of novel pharmacotherapeutics as  
5 adjunct to lifestyle interventions in reducing CV risk trajectories.

6 An overview on key management strategies to lower childhood CV trajectories including the  
7 main challenges and key barriers are shown in **Table 2**. With respect to developing screening  
8 programs for primary prevention of obesity-related CV risk, it remains to be determined who,  
9 when and how to screen in order to identify children at risk and most in need for early treatment  
10 interventions. From a public health perspective, no reliable data are available on how these  
11 prevention strategies in childhood may be cost effective. Although there has been an increase  
12 in the number of school-based childhood obesity interventions in recent years,<sup>124</sup> there is a  
13 need for longer follow-up in these studies to assess the sustainability and cost-effectiveness  
14 of any related reductions in BMI z-scores. Similarly, research into these interventions has not  
15 provided definitive results regarding whether there are improvements in BP, glucose and lipid  
16 metabolism or markers of target organ damage such as vascular biomarkers, which should be  
17 adopted into ongoing and future work in this area. Different types of lifestyle interventions also  
18 need further study, including direct comparison of types of aerobic exercise training programs  
19 – such as high intensity interval training versus moderate intensity continuous training<sup>125</sup> – and  
20 how they are delivered – such as in person, remotely, and/or via mobile apps<sup>126</sup>. To date, it is  
21 unclear at what time during childhood development specific lifestyle interventions may be most  
22 effective. As mentioned, exergaming may be a feasible way to attract children and adolescents  
23 to engage more in PA and exercise.<sup>87</sup> Several apps have been developed in recent years and  
24 are readily available to support implementation of PA programs. Most of these apps have been  
25 designed for adults and more research is needed to investigate the potential for use in children  
26 and adolescents and to help guide healthy lifestyle early in life. The potential for school-based  
27 educational programs on the interrelation between PA and health and the potential use for  
28 exergaming strategies needs to be investigated in future research.

29 It will be of utmost importance to investigate how well any exercise-induced CV and metabolic  
30 benefits translate into longer term health improvements in adulthood. Similarly, how PA and  
31 dietary interventions impact on specifically lowering visceral adipose tissue remains to be more  
32 precisely determined. While pharmacological treatments such as semaglutide have shown to  
33 be effective for sustained body weight reduction in adult populations with obesity<sup>127</sup>, our  
34 understanding of the efficacy and safety in childhood and adolescent obesity is limited.  
35 Furthermore, how drugs such as semaglutide may benefit long-term CV physiology and  
36 metabolism is still an ongoing question even in adult populations.<sup>128</sup> Determining which drug



1 therapies are needed for which individuals will be an important step for clinical implementation  
2 but will first require a better understanding of their potential efficacy and long-term benefits and  
3 risks. Furthermore, understanding whether pairing lifestyle interventions with pharmacological  
4 therapies improves efficacy needs to be incorporated into future work streams.

5 An area of immediate need is a push to increase awareness among the clinical community,  
6 parents, and society regarding the complexity of underlying causes of childhood obesity and  
7 associated CV risk. Part of this need is to reduce stigmatization that may impact on quality of  
8 life and be a driving stimulus for the development of eating disorders and physical inactivity. In  
9 line with this, there is a lack of consistent governmental support in school-based settings for  
10 health promotion and interventions,<sup>129</sup> including physical education curricula and availability of  
11 high-quality school meals. Further focus needs to be placed on executing policies for healthy  
12 nutrition standards and access to appropriate facilities and well-trained teachers to improve  
13 engagement with a healthy lifestyle. One of the main challenges in promotion of healthy  
14 behaviors remains local and national discrepancies in government support in limiting  
15 production and marketing of unhealthy, energy dense foods and increasing access to healthy  
16 foods at lower costs. It is thus of immediate public health importance that governments and  
17 policymakers adopt changes to these current societal limitations, with appropriate adoption of  
18 tools to measure their success in practice.

## 19 **8. Conclusions**

20 In summary, there is a severe need to invest in screening and treating obesity-related CV  
21 disease risk in children and adolescents to counteract the associated CV disease burden later  
22 in life. Considerable evidence suggests that multicomponent behavioral programs including  
23 exercise and diet have the potential to improve obesity-related CV risk and associated risk  
24 trajectories into adulthood. This scientific statement can be considered a “global call for action”  
25 for implementation of such screening programs and consecutive multimodal lifestyle  
26 interventions in children at risk in order to reduce their cumulative lifetime risk. Before such  
27 programs can be routinely implemented on a population-level, further evidence for their long-  
28 term efficacy and relative cost effectiveness, for example in terms of quality-adjusted life years,  
29 is warranted. Despite the urgent need for more conclusive evidence on the benefits and pitfalls  
30 of long-term screening and sustainability of treatment effects, we believe research programs  
31 and prevention strategies of local, national and international authorities should aim at  
32 facilitating the necessary infrastructure based on “lessons learned” from the presented  
33 evidence. To facilitate primary prevention “action plans” early in life should be favored over a  
34 “wait and see” approach, which is deemed to cause an ever-growing burden of CV disease  
35 and a socioeconomic hazard on health care systems and society.

36

1 **Conflict of interest:** Giuseppe Biondi-Zoccai has consulted for Cardionovum, Cranmedical,  
2 Innovheart, Guidotti, Meditrial, Opsens Medical, Replycare, Teleflex, and Terumo. Daniel  
3 Weghuber has received consulting and lecturing fees from Novo Nordisk A/S. Maja-Lisa  
4 Løchen has received lecture fees from Bayer, Sanofi and BMS/Pfizer.

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1 **Figure Legends**

2 **Figure 1.** Aetiology of obesity-related cardiovascular (CV) risk highlighting the complex  
3 interplay between societal, psychological, environmental and biological factors. EDCs:  
4 Industrially produced endocrine-disrupting chemicals.

5 **Figure 2.** Call for action concept: implementation of childhood screening and prevention  
6 programs to change risk trajectories of obesity-related cardiovascular risk from childhood to  
7 adulthood.

Figure 1.

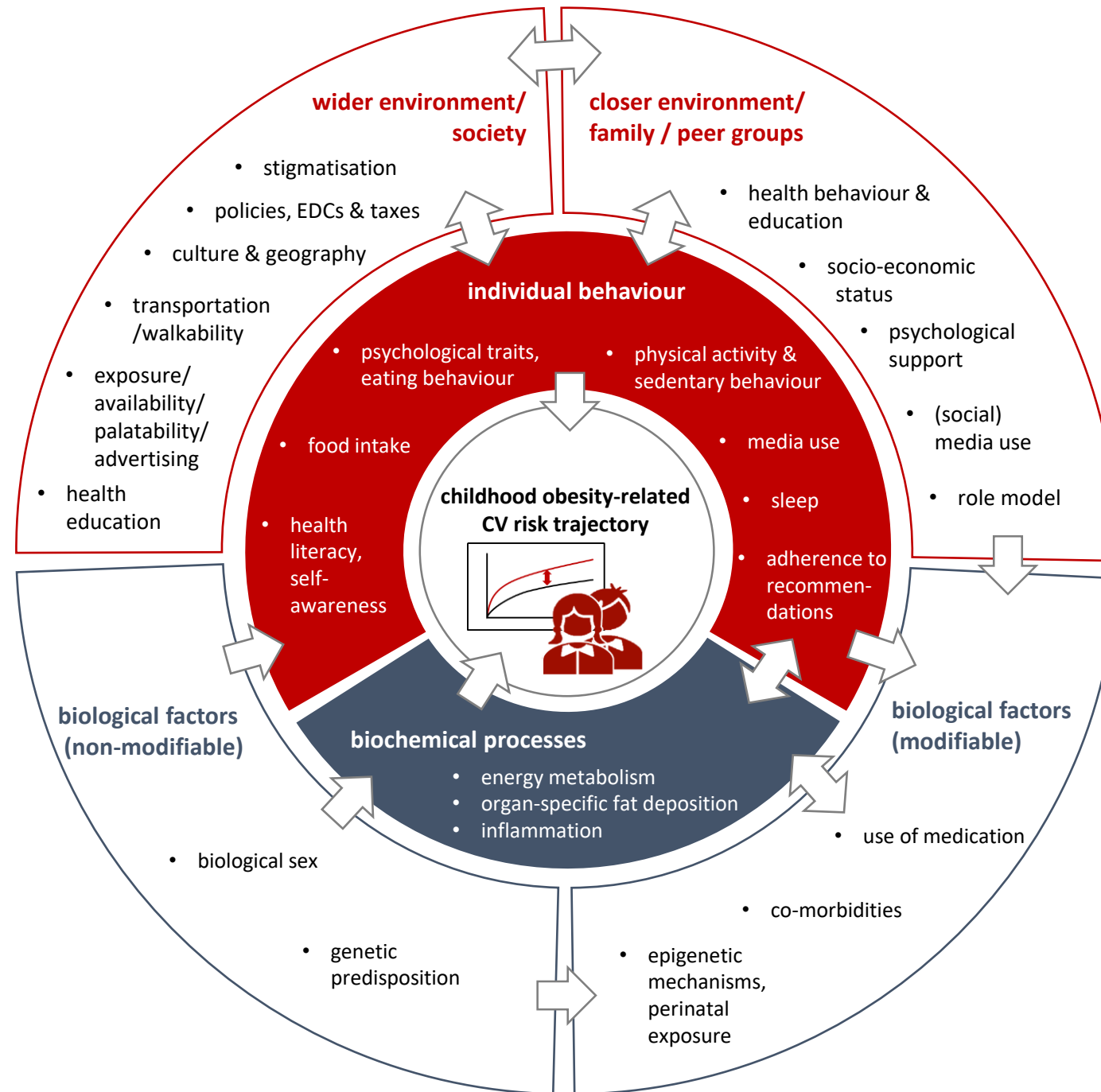


Figure 2.

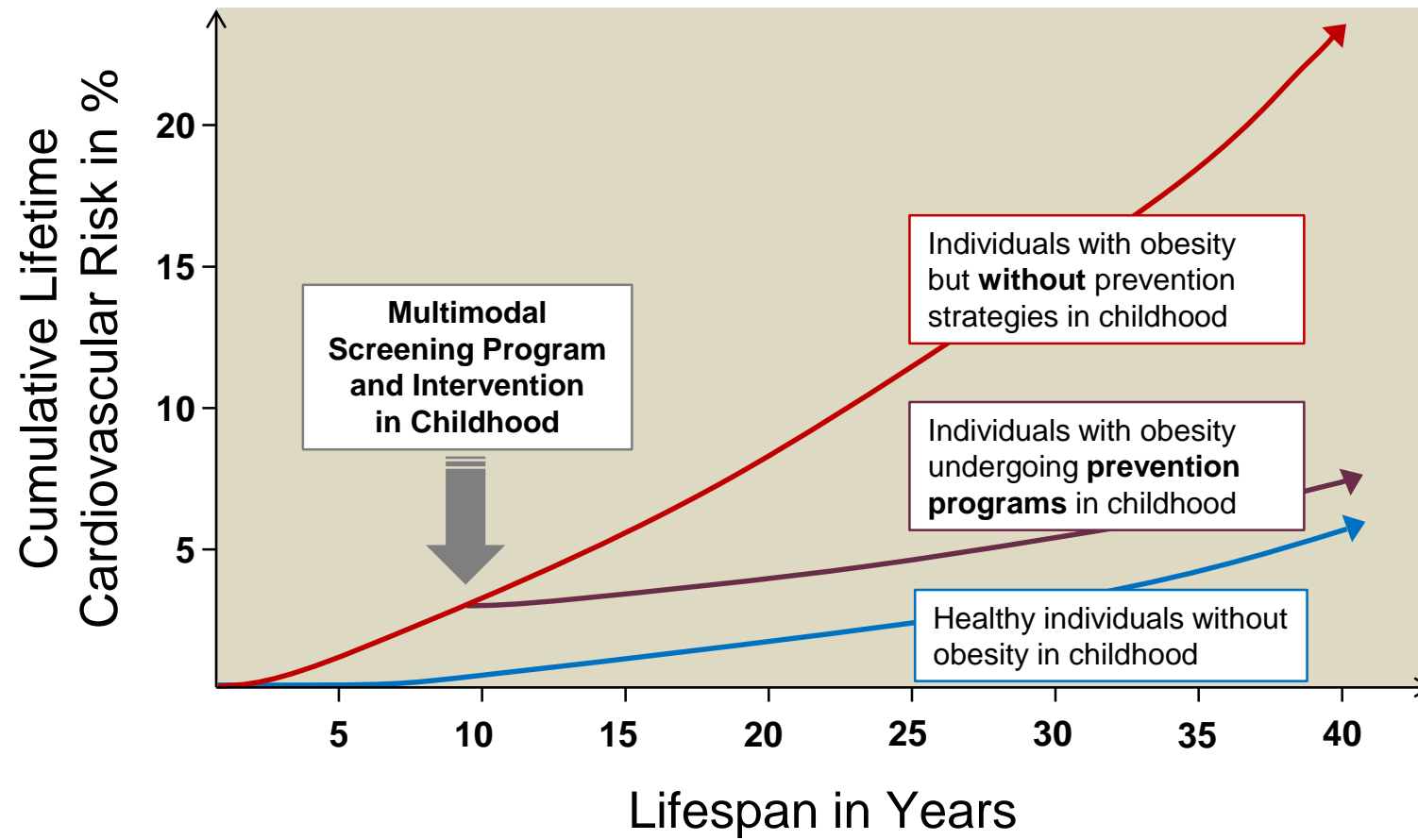


Table 1. Definition and thresholds of childhood cardiometabolic risk factors

<b>Cardiometabolic risk factors</b>	<b>Definition</b>
Overweight and obesity	<ul style="list-style-type: none"> <li>• Age- and gender-specific percentile curves based on national reference population <b>or</b></li> <li>• Cut-off values for overweight and obesity according to International Obesity Task Force (IOTF), World Health Organization (WHO), or Center for Disease Control (CDC)</li> </ul>
Hypertension	<ul style="list-style-type: none"> <li>• 0-15 years: ≥ 95th percentile for systolic (SBP) and diastolic blood pressure (DBP) (according to sex-age-height-specific percentiles)</li> <li>• 16 years and older: ≥ 140/90 mm Hg (SBP and/or DBP values)</li> </ul>
Dyslipidemia	<ul style="list-style-type: none"> <li>• Total Cholesterol ≥ 200 mg/dL</li> <li>• Low-density lipoprotein (LDL) cholesterol ≥ 130 mg/dL</li> <li>• High-density lipoprotein (HDL) cholesterol &lt;40 mg/dL</li> <li>• Triglycerides (TG) ≥ 100 mg/dL &lt; 9 years</li> <li>• TG ≥ 130 mg/dL ≥ 10 years</li> </ul>
Hyperglycemia	<ul style="list-style-type: none"> <li>• Fasting blood glucose ≥ 100 mg/dL <b>or</b></li> <li>• Glycated hemoglobin (HbA1c) ≥ 5.7%</li> </ul>
Physical inactivity	<ul style="list-style-type: none"> <li>• &lt; 60 min/day moderate/vigorous physical activity</li> <li>• sedentary behavior ≥ 2 h/day</li> </ul>

Table 2. Overview on key management strategies to lower childhood cardiovascular risk trajectories

<b>Prevention and screening strategies</b>
✓ Focus on clustering of risk factors
✓ Screening for overall cardiovascular risk including psychological factors
✓ Screening programs from childhood into adulthood
✓ Include family and peers in addition to school-based education
✓ Governmental support for population-based education campaigns
✓ Promote awareness for role of parenting style for physical activity and nutrition behaviour
✓ Avoid stigmatization
<b>Management strategies of multicomponent behavioural interventions</b>
✓ Promotion of physical activity and exercise
✓ Raise awareness for the need to reduce physical inactivity
✓ Promotion of healthy eating habits
✓ Accessibility to diet counselling
✓ Reduce unhealthy food marketing in media and social media
✓ Psychological support for behaviour change
✓ Built environment: accessibility and affordable infrastructure for healthy foods and physical activity in urban settings
✓ Smoking cessation and alcohol avoidance
✓ Sleep hygiene
<b>Key barriers</b>
✓ Evidence-base for sustainability of interventions
✓ Evidence-base for cost-effectiveness
✓ Financing of prevention programs