Obesity and metabolic syndrome

Lifetime risk: childhood obesity and cardiovascular risk

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In a recent report, the worldwide prevalence of childhood obesity was estimated to have increased by 47% between 1980 and 2013. As a result, substantial concerns have been raised about the future burden of cardiovascular (CV) disease that could ensue. The purpose of this review is to summarize and interpret (i) the evidence linking early life obesity with adverse changes in CV structure and function in childhood, (ii) the lifetime risk for CV disease resulting from obesity in childhood, and (iii) the potential effects of lifestyle interventions in childhood to ameliorate these risks.

Keywords
Obesity • Cardiovascular risk

Prevalence and trends

The prevalence of childhood overweight and obesity has increased dramatically, in both developed and developing countries, over the last 30 years. A recent report, which combined many sources of data, estimated that the worldwide prevalence of childhood obesity had increased by 47.1% between 1980 and 2013.¹ The most marked rise occurred in developed countries; in 1980, 16.9% of boys and 16.2% of girls were classed as overweight or obese but this had increased to 23.8 and 22.6%, respectively, by 2013. An important increase in this prevalence has also been occurring in the developing world, from 8.1 to 12.9% in boys and 8.4 to 13.4% in girls, over the corresponding time. This high and increasing prevalence of childhood overweight and obesity mirrors trends in adults. Despite lower prevalence rates than in many Western countries, populous ‘emerging’ countries such as China and India face a major burden of childhood obesity now and potentially into the future. Data from recent U.S. national surveys suggest a recent plateau of the prevalence of childhood overweight and obesity.² However, even here, the overall levels remain disturbingly high and there is significant geographical variation in the trends.³ Furthermore, the prevalence of childhood overweight and obesity is related to poverty and ethnicity,⁴ making the imperative to reduce obesity prevalence in childhood an issue of social justice, as well as a medical and health economics problem.

Definitions of childhood obesity

Obesity is characterized by an excess of body fat which confers an increased risk of adverse health outcomes. Body fat may be estimated by a number of techniques (Table 1), each with different strengths and limitations. Percent body fat (%BF) may be estimated by dual energy X-ray absorptiometry (DXA). As DXA is not widely available outside a research setting, the association of other, more easily obtainable, measures with %BF and their cut-points with health risks have been evaluated. In children, skin fold thickness (SFT) correlates reasonably strongly with %BF but its reproducibility is poor, particularly for single SFT measurements. Body mass index (BMI, kg/m²), although a more practical and reproducible measure and the most widely reported estimate of adiposity, is relatively insensitive in discriminating between lean body mass and fat mass. In children, the association between BMI and %BF is dependent upon race/ethnicity and may not account for other factors that influence weight-for-height, such as prior undernutrition. Definitions and estimates of prevalence rates of childhood overweight and obesity are based upon comparison with BMI reference values, which are available, for example, from the World Health Organization, U.S. Centres for Disease Control and Prevention and The International Obesity Taskforce (IOTF). The ability of any of the various childhood BMI cut-offs to predict the presence of

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adipose tissue appears to convey the highest cardio-metabolic risk in the routine assessment of overweight or obese children. It seems reasonable to include WC measurement and WHtR calculation in children and obese youth. Despite these current uncertainties, it would appear that WC, as it does not require conversion to a percentile, may help to define a metabolic healthy group of overweight and obesity cut-offs in predicting adult hypertension and hyperlipidaemia.5

Excessive visceral adipose tissue (VAT) rather than subcutaneous adipose tissue appears to convey the highest cardio-metabolic risk in adults.6 Waist circumference (WC) appears to contribute to the prediction of abdominal fat, to a similar degree as BMI.7 In children, the waist : height ratio (WHtR) may be a more practical measure than WC, as it does not require conversion to a percentile. Waist circumference and WHtR have been shown to predict cardio-metabolic risk over and above BMI in some but not all studies of children and these measures may help to define a metabolic healthy group of overweight and obese youth.8–10 Despite these current uncertainties, it would seem reasonable to include WC measurement and WHtR calculation in the routine assessment of overweight or obese children.

**CV effects of obesity in children**

**Endothelial function and arterial stiffness**

Endothelial dysfunction is a key early step in the development of CV disease and may be assessed non-invasively using techniques such as brachial artery flow-mediated dilatation (FMD). Increased arterial stiffness, associated with an increased risk of CV disease in adults, occurs with aging itself but may also be a result of higher levels of certain CV risk factors. An indication of arterial stiffness may be gained by measurements of the compliance or distensibility of an arterial segment, the speed of transit of the pulse wave (pulse wave velocity, PWV) or the timing and magnitude of wave reflection (pulse wave analysis). Several smaller studies have demonstrated reduced FMD and increased arterial stiffness in obese compared with lean children and adolescents.11–21 These studies have largely compared FMD and arterial stiffness between either severely (BMI z-score > 2.0) and/or older (> 10 years) obese children and lean controls.

In a large study of children and young adults (age range 10–24 years) referred to a hospital clinic, Urbina et al. measured endothelial function and arterial stiffness in lean controls (n = 241) and obese subjects without (n = 234) and with (n = 241) type 2 diabetes.22 There was a progressive deterioration in endothelial function and arterial stiffness from lean; to obese; to obese with type 2 diabetes, which remained after adjustment for CV risk factors. In a large cohort of 10 and 11 year olds in the Avon Longitudinal Study of Parents and Children (n = 6576, 80% normal weight, 16% overweight, and 4% obese by IOTF criteria), overweight and obese children had worse metabolic profiles, better endothelial function and reduced arterial stiffness compared with normal weight children.23 The overweight and obese children had a higher heart rate, greater resting and reactive hyperaemic blood flow, and larger brachial artery diameter, suggesting an adaptive hyperaemic state in response to pre-pubertal adiposity. However, when overweight/obese (n = 28) and lean (n = 14) subjects were studied at age 14 and again at 19 years, there was a significantly greater increase in PWV over 5 years in the overweight/obese (25% compared with 3% in the lean adolescents) despite similar baseline PWV.24

Taken together, it is possible to speculate that there is an early stage of ‘vascular adaptation’ that may be overcome with either more severe or longer duration of obesity, the influence of puberty...
development or the onset of type 2 diabetes. The effects of these interactions remain to be clarified.

**Arterial wall thickness**

Structural changes in the arterial wall may be assessed on ultrasound by measurement of intima-media thickness (IMT). In adults, IMT is correlated with coronary and carotid atherosclerosis and is a significant predictor of future CV events. In children, IMT is increased in children at high risk for future CV disease, such as those with familial hypercholesterolemia and type 1 diabetes mellitus.

Several studies have reported higher IMT in obese compared with lean children and adolescents.11,16–19,21,25 Once again these studies have largely been in older children and adolescents and in the significantly obese. Other studies have not demonstrated a difference in IMT despite changes in endothelial function or arterial stiffness.14,20

A cumulative burden of childhood obesity and/or interaction with aging, puberty, and other CV risk factors may be required to produce differences in arterial structure.

Furthermore, whether childhood obesity is independently associated with arterial wall thickness in adulthood is uncertain. For example, longitudinal data from the Young Finns Study demonstrated an association between childhood BMI and adult IMT, which was significantly attenuated or abolished after adjustment for adult BMI.26–28

As with effects on endothelial function and arterial stiffness, arterial wall remodelling in obesity may be influenced by the duration and severity of obesity, the interaction of ‘obesity’ with other CV/metabolic risk factors and also by pubertal development.

**Cardiac structure**

Left ventricular mass (LVM), a quantitative assessment of the thickness of left ventricular muscle, is an independent risk factor for CV morbidity and mortality.29 A number of studies have demonstrated increased LVM in obese children and adolescents compared with normal weight controls30–32 and increasing LVM with increasing childhood BMI.33 Although both LVM and BMI track from childhood into adulthood, the strength of the association between BMI and LVM appears to increase with age.33 Furthermore, in a study of 467 young adults, Li et al. found that the significant independent determinants of adult LVM were childhood BMI, current BMI, and systolic BP and the ‘cumulative burden’ of BMI from childhood to adult life.34 The influence on LVM of body composition (lean vs. fat mass) remains controversial and may differ in overweight/obese compared with normal weight children and may also vary by gender.35–37 A central distribution of fat appears to be more highly correlated with LVM in children.30,38

Left atrial size is independently associated with a higher risk of atrial fibrillation, stroke, heart failure, and death in adults.39 Several studies have demonstrated an association between BMI and left atrial (LA) size in childhood40–42 and higher LA size in overweight/obese than normal weight children.43 Tracking of LA size from childhood to adult life and the strength of the association between childhood BMI and adult LA size adjusted for adult BMI remain to be determined. Evaluation of atrial phasic function with atrial strain has not been reported in obese children. The relationship, however, between LA size and obesity may relate to abnormalities in ventricular mechanics, particularly diastolic dysfunction, which has been documented in asymptomatic obese adults44,45 and children.36–48 The degree of tracking of these abnormalities in ventricular mechanics from childhood into adulthood also remains to be determined.

Taken together, these data suggest that childhood obesity has an important effect on cardiac structure which persists into adult life and may accentuate the cardiac effects of adult obesity.

**Risk factor clustering in obesity**

A number of studies have demonstrated that risk factors for CV disease, such as high blood pressure, cholesterol, diabetes, and overweight/obesity, cluster together in children and adolescents and are significantly inter-correlated.49 The statistical techniques of principal components analysis reduce these risk factors into a smaller number of summary factors, while retaining as much variance as possible in the original variables. This appears to be a valid way to evaluate the underlying determinants of CV disease risk. For example, in a study of 1578 adolescents, Goodman et al. describe four such uncorrelated summary risk factors: adiposity (including BMI, waist, fibrinogen, and insulin), cholesterol (including low density lipoprotein- and total cholesterol), carbohydrate-metabolic (including glucose, insulin, high density lipoprotein (HDL)-cholesterol, and triglycerides), and blood pressure (including systolic and diastolic BP).49 Such principal components analyses suggest that obesity (and perhaps to a lesser extent hyperinsulinemia) is the most important correlate for being at high risk for each of these summary factors.

A particular pattern of risk factor clustering characterises the metabolic syndrome (MetS). Although a standard definition for paediatric MetS has been lacking until recently, some combination of increased WC plus 2 or more of elevated triglycerides, low HDL-cholesterol, hypertension, and glucose intolerance has been included in most studies. Does a definition of MetS in youth help with defining CV risk, over and above an analysis of the independent risk factors for CV disease? Some50–52 but not all53 studies have demonstrated greater alterations of CV structure and function in obese children with MetS compared with obese children without MetS. Although paediatric MetS predicts adult MetS and increased adult IMT, it is no better at doing so than childhood BMI.44 Furthermore, childhood-MetS which resolves in adulthood does not convey an increased risk of high adult carotid IMT or type 2 diabetes.55

Longitudinal data from four large prospective cohorts indicate that adult IMT increases with the number of childhood CV risk factors measured after age 9 years.28 However, further data from long-term cohort studies are required on whether risk factor clustering in childhood predicts the development of CVD in adults. Available data support the notion that consideration of risk factor clustering in children is important for determining future CV risk.

**Mechanisms of CV dysfunction in childhood obesity**

The cumulative burden of ‘traditional’ CV risk factors that accompany obesity may alter early steps in atherosclerosis (endothelial function, arterial stiffness, adhesion molecule expression, foam cell formation, and smooth muscle proliferation) as well as later changes (plaque rupture and thrombosis). However, recent studies have focussed on novel mediators of CV dysfunction in obesity. Dysfunctional VAT (as part of an ‘adiposopathy’), in particular, may be an important
source of mediators of inflammation, oxidative stress, and angiogenesis (Figure 1). These mediators, known as adipocytokines, may act locally in an autocrine or paracrine manner or more distantly, in an endocrine fashion. Although a detailed discussion is beyond the scope of this review, there is a growing body of evidence linking various adipocytokines, including leptin, resistin, adiponectin, interleukin-6, and tumour necrosis factor-α, to different steps in the development of CV disease. Much work has been done to define the role of athero-inflammation of adiponectin, a 244-amino acid protein which is produced principally by white adipose tissue and which is paradoxically found in lower levels in obese compared with non-obese subjects.56,57 Physiological levels of adiponectin inhibit monocyte adhesion to human aortic endothelial cells, down-regulate the expression of adhesion molecules on these endothelial cells,58 suppress human aortic smooth muscle cell proliferation and migration,59 inhibit macrophage foam cell transformation,60 and increase the production of tissue inhibitor of metalloproteinase-1 (an important regulator of extracellular matrix degradation and atherosclerotic plaque rupture).61 Apo-E deficient mice treated with recombinant adenovirus that expresses human adiponectin show significantly less atherosclerosis than control Apo-E deficient mice.62 In human studies, low adiponectin levels have been associated with greater levels of hs-CRP,63 endothelial dysfunction in adults and children,64 greater progression of coronary artery calcification,65 thicker carotid IMT in adolescents,66,67 and women.68 These studies have shown that actions of adiponectin are consistently anti-atherosclerotic.

Reversibility of adverse CV effects of childhood obesity

Intensive lifestyle interventions, of healthy eating, exercise, and reducing sedentary activity, are the cornerstones of treatment of obesity in childhood and adolescence. Clinical trials of lifestyle interventions in adults report a weight-loss efficacy of between 5 and 10%, often resulting in important improvements in CV risk factors. However, such efficacy is rarely seen in the primary care setting and long-term weight maintenance remains a problem. Paediatric lifestyle intervention trials have also reported improvements in body composition and metabolic parameters. Several paediatric studies have shown improvements in FMD and/or IMT with diet alone,69 exercise alone70–73 or diet and exercise (Table 2).69

A recent review of adult outcomes after bariatric surgery supported a benefit on CV mortality and morbidity. Several studies have reported benefits of bariatric surgery on CV risk factors, endothelial function, IMT progression, LV mass and function. In adolescents, bariatric surgery has been recommended as an adjunct to lifestyle interventions with BMI > 40 kg/m² plus a severe co-morbidity or BMI > 50 kg/m² and a less severe co-morbidity.74 Although bariatric surgery has been shown to reverse the metabolic complications and cardiac structural and functional changes of severe adolescent obesity, few other reports of its long-term effects on CV health in youth have been reported.75

A number of weight-loss drug therapies have been approved for use in adults worldwide, including orlistat, lorcaserin, and

Figure 1 Schematic of the complex pathophysiology of CVD in ‘adiposopathy’ of obesity.
phentermine plus topiramate-ER. The evidence of the impact of these medications in children and adolescents on weight loss is limited and little, if any, data are available on their CV effects at this age. Metformin appears to improve insulin resistance and other metabolic markers in obese adolescents.

**Childhood obesity and lifetime CV risk**

Estimating the lifetime risk for obese children has been challenging as most of the information is derived from observational studies. In a cohort of children born in Denmark a higher BMI in childhood was associated with increased risk for coronary heart disease in adulthood. A 55-year follow-up of the Harvard Growth Study showed that being overweight in adolescence resulted in a 2-fold higher risk of coronary heart disease mortality which was independent of adult weight. A British study that involved a 57-year follow-up of a cohort also confirmed that all-cause and CV mortality were increased when childhood BMI was higher than the 75th centile. More recently, in the Bogalusa Heart Study elevated blood pressure and adiposity from childhood onwards had an adverse effect on LVM and geometry in 1061 subjects. Even if the prevalence of obesity in the young can be reduced, a substantial number of children who are currently overweight or obese will grow up to be obese adults. Achieving sustained weight loss is a challenge. The predicted risk of adult weight. A British study that involved a 57-year follow-up of a cohort also confirmed that all-cause and CV mortality were increased when childhood BMI was higher than the 75th centile. More recently, in the Bogalusa Heart Study elevated blood pressure and adiposity from childhood onwards had an adverse effect on LVM and geometry in 1061 subjects. Even if the prevalence of obesity in the young can be reduced, a substantial number of children who are currently overweight or obese will grow up to be obese adults.

**Clinical implications**

Current data indicate that obesity unfavourably alters CV structure and function during childhood and adolescence itself. Childhood obesity also appears to confer an increased lifetime risk for CV disease. These data highlight the major CV health opportunities that are likely to arise from the development and implementation of strategies that reduce the prevalence of childhood overweight and obesity. Appropriately, the greatest medical focus will be on the development of ‘treatments’ for severely obese children and adolescents with the highest future CV risk and most abnormal CV structure and function. However, the greatest population burden of CV disease will be driven by those with lesser degrees of excess adiposity. Here, the development of unifying strategies to address both childhood and adult obesity will be made harder by environmental, cultural, and economic factors that promote increased caloric intake and sedentary lifestyles. Recently, strategies for the prevention and management of obesity in early life have been the subject of several national public health guidelines. Implementation of these guidelines will require a concerted effort of many stakeholders, which will include politicians, infrastructure planners, physicians, scientists, and other professionals to convey the ‘lifetime risk’ message to families and to support the early management of childhood obesity.

**Future directions**

There remain substantial gaps in our understanding of the development of CV disease in children and adolescents who are overweight or obese. It remains uncertain how best to measure clinically the CV risk in the young. What measurements undertaken at what time points in childhood best predict CV disease in adult life? Other than LVM, clinical measurements of adverse CV alterations are not yet available and it is unclear whether routine assessment of endothelial function, arterial stiffness, ventricular wall thickness, or mechanics will help to stratify risk in children and whether those measures will support more aggressive therapy, including weight-loss medication.

**Table 2** Studies examining the effects of interventions to reduce obesity on cardiovascular structure and function in children

<table>
<thead>
<tr>
<th>First author, year (Ref. no.)</th>
<th>Type(s) of intervention(s)</th>
<th>Number(s) in intervention group(s)</th>
<th>Number in non-intervention group</th>
<th>Age (years)</th>
<th>Intervention duration (month)</th>
<th>Cardiovascular effects: intervention vs. non-intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farprou-Lambert, 2009</td>
<td>Exercise</td>
<td>22</td>
<td>22</td>
<td>8.9 ± 1.5</td>
<td>3 + further 3 open label</td>
<td>↓ BP, ↓ fat, ↑ fitness (3 months), ↑ BP, ↓ IMT, ↓ arterial stiffness, no effect on FMD (6 months)</td>
</tr>
<tr>
<td>Woo, 2004</td>
<td>Diet only or diet + exercise</td>
<td>41</td>
<td>–</td>
<td>9.9 ± 1.0</td>
<td>1.5</td>
<td>↑ FMD</td>
</tr>
<tr>
<td>Kelly, 2004</td>
<td>Exercise</td>
<td>10</td>
<td>10</td>
<td>–</td>
<td>2</td>
<td>↑ FMD</td>
</tr>
<tr>
<td>Watts, 2004</td>
<td>Exercise</td>
<td>19</td>
<td>19</td>
<td>14.3 ± 1.5</td>
<td>2</td>
<td>↑ FMD</td>
</tr>
<tr>
<td>Meyer, 2006</td>
<td>Exercise</td>
<td>33</td>
<td>34</td>
<td>14.7 ± 2.2</td>
<td>6</td>
<td>↑ FMD, ↑ IMT</td>
</tr>
<tr>
<td>Watts, 2004</td>
<td>Exercise</td>
<td>14</td>
<td>14</td>
<td>8.9 ± 0.4</td>
<td>2</td>
<td>↑ FMD</td>
</tr>
<tr>
<td>Ippisch, 2008</td>
<td>Bariatric surgery</td>
<td>38</td>
<td>–</td>
<td>16 ± 1.0</td>
<td>10</td>
<td>↓ BP, ↓ LVM, ↑ diastolic function</td>
</tr>
<tr>
<td>Mitchell, 2002</td>
<td>Exercise</td>
<td>20</td>
<td>15</td>
<td>13–16</td>
<td>8</td>
<td>No effect on LVM</td>
</tr>
</tbody>
</table>

BP, blood pressure; IMT, intima-media thickness; FMD, flow-mediated dilatation; LVM, left ventricular mass.
or bariatric surgery. Larger cross-sectional measurements of these parameters in healthy children to derive population norms will be helpful. Although childhood obesity appears to convey a lifetime risk for CV disease, it remains unclear as to what factors during the passage through childhood into adult life may influence this risk. Large-scale multi-ethnic longitudinal studies, undertaken preferably from birth but certainly from early childhood, are required to study these factors. Measurements should preferably include more detailed assessments of body composition and fat distribution and pubertal development. Some lifestyle intervention studies have indicated reversibility of adverse CV structure and function over a short or intermediate time frame. The long-term effects on CV risk and disease of lifestyle interventions, drug therapies, and bariatric surgery in children and adolescents remain to be determined.

Conclusions

Considerable evidence exists for adverse effects of childhood obesity on CV structure and function. Evidence also exists for childhood obesity conferring an increased lifetime risk for CV disease. Further research is required on factors which may interact with obesity to alter this risk. However, sufficient information is available to be concerned about the future burden of CV disease that childhood obesity entails. Such data support the call to arms to develop better therapies to manage childhood obesity and society wide changes to reduce its prevalence.

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References

Childhood obesity and cardiovascular risk


