Metabolic syndrome unravelling or unravelled?

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Abstract

Metabolic syndrome (MS) is a composite of risk factors for cardiovascular disease including dyslipidaemia, insulin resistance, hypertension and usually associated with obesity. Initially MS was considered a condition of adults but is now recognised as having a prevalence of approximately 3.3% in children. The clinical relevance of MS in children is currently unknown but the morbidity associated with childhood obesity is well-recognised. This review describes the epidemiology of childhood MS, the underlying risk factors, possible developmental mechanisms and gives an overview of the current management of obesity in children.

Keywords epidemiology; fetal development; longitudinal studies; metabolic syndrome; obesity

Introduction

The metabolic syndrome (MS) is a composite of clinical features which are also risk factors for adult cardiovascular disease and can be defined as a combination of obesity, dyslipidaemia, insulin resistance and hypertension. The MS is an asymptomatic condition which might be thought of as "pre-diabetes". Initially MS was considered a condition of adults but since the late 1990s has been identified in children, by either extrapolating adult criteria to the younger age group or by creating child-specific criteria. There remains some controversy about how best to define MS in children but the most widely accepted criteria for defining MS in children according were produced by the International Diabetes Federation in 2007 (Table 1). Outwith the diagnostic uncertainty of MS, there are a number of apparent inconsistencies with counter-arguments concerning MS (see Table 2).

As the prevalence of childhood obesity rises, there are concerns that this will lead to a chain of events whereby childhood MS prevalence rises which persists into adulthood resulting in an "epidemic" of type 2 diabetes and cardiovascular pathology. This bleak prospect is by no means certain as MS in children can apparently resolve over time and until children with MS are followed up into mid and late adulthood, where the burden of cardiovascular disease is most apparent, we cannot be certain of the importance of MS in childhood. However, there is justifiable reason to anticipate that there will be an increased burden of morbidity from MS among today's children when they reach adulthood as obesity prevalence is approximately three times higher in the 2000s compared to the 1980s.

Here we aim to summarise developments in epidemiology, explore the underlying mechanisms and provide an update on clinical management.

Epidemiology of metabolic syndrome

Historically it has been challenging to study the epidemiology of MS due to the absence of a single universally accepted definition. The five consistent criteria for MS diagnosis are: 1. obesity, 2. elevated triglycerides, 3. reduced high density lipoprotein, 4. hypertension and 5. raised fasting blood glucose (or index of insulin resistance). The World Health Organisation (WHO) definition stated that hyperglycaemia was an essential criterion but two additional "abnormal" results out of the remaining four criteria were also required, whereas the International Diabetes Federation (IDF) placed obesity as the essential criterion and the National Cholesterol Education Program Adult Treatment Panel (ATP) were more permissive and allowed any three "abnormal" criteria. These three definitions (i.e. WHO, IDF and ATP) have been subtly amended over time by research groups yielding at least 40 different definitions with each inevitably yielding a different estimate of prevalence. For example, one study applied 14 definitions to the same population and reported an incidence of MS which varied between 0.4 and 24% whilst in second study population, MS prevalence varied between 0 and 60% depending on which criteria were applied. Central to this apparent confusion is uncertainty as to what is "normal" for children. For example, for obesity the 85th and 95th body mass index (BMI) centiles are usually used to define overweight and obesity in epidemiological studies but 91st and 98th centiles are usually applied in clinical practice, however waist circumference (an index of abdominal obesity) is thought to be a more appropriate measure of excessive body fat. Puberty further complicates the situation by normally increasing body fat distribution (more so in girls than boys) and also insulin resistance. The widely accepted IDF criteria for diagnosing MS in children aged 10–16 are very helpful in understanding the epidemiology from 2007 onwards (Table 1).

International Diabetes Federation diagnostic criteria for children aged 10–16 years

Overall Requirement	Obesity plus ≥2 other "abnormal" results
Obesity	Waist circumference ≥90th centile
Triglyceride	≥1.7 mmol/Litres
High density lipoprotein	<1.03 mmol/Litres
Systolic hypertension	≥130 mmHg
Plasma glucose	≥5.6 mmol/Litres

Table 1

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Apparent inconsistencies in the Metabolic Syndrome

Apparent inconsistency	Counter argument(s)
The majority of obese children do not have MS	There are different obesity phenotypes
There are non-obese children with MS	Obesity may not be causally related to MS
Reduced birth weight is associated with all features of MS apart from obesity	
If fetal origins are implicated why are effects not apparent from early life	An interaction between antenatal and postnatal factors leads to MS
	The duration of obesity may be relevant to the development of MS
MS can resolve in some children	The criteria previously used were not robust
	Changes in lifestyle may reverse MS

Table 2

Risk factors

A recent systematic review (2013) including data from 85 papers, concluded that the median prevalence of MS was 3.3% for children but there was considerable variability observed between different populations. These differences in prevalence between populations were partly explained by the criteria used, generally ATP-based criteria yield higher prevalence than IDF-based criteria. There are four clear risk factors for MS: 1. Weight, 2. Sex, 3. Age and 4. Geography.

Weight appears to be the most important single risk factor. MS is mostly restricted to overweight and obese children where the typical prevalences were 12% and 29% respectively; MS prevalence in the non-overweight and non-obese population was between 0 and 1%. The second risk factor for MS is sex, with boys having increased prevalence compared to girls (median prevalences are 5.2% and 3.1% respectively). A third established MS risk factor is increasing age and, where MS prevalence is reported for age groups within populations, the median prevalences are 2.9% and 5.6% for younger and older children respectively. A final risk factor for MS prevalence is geography; median prevalence is highest in Middle East countries (approximately 6%) and lowest for European countries (approximately 2%) with intermediate values for the Americas (between 3 and 4%) and the Far East (approximately 3%). The geographical differences might point towards MS being associated with ethnic groups, and although some studies find differences (for example higher prevalence among white Americans compared to African Americans) there is no consistent association.

Prevalence over time

Obesity is closely associated with MS and, given the rise in childhood obesity prevalence, there is concern that MS prevalence will also rise. There are very few studies whose results can help answer the question "is MS prevalence rising?" and this reflects both the uncertainty of diagnostic criteria and also the relatively recent emergence of MS as a paediatric condition. The previously mentioned review identified four studies which reported on MS prevalence measured in repeated cross-sectional studies (Figure 1) and between 1992 and 2005 there was no evidence of increases in MS prevalence despite there being two to three fold increases in childhood obesity prevalence during this period.

Pathophysiology of metabolic syndrome

Cohort studies have identified associations between reduced birth weight and increased risk for cardiovascular disease and components of the MS including insulin resistance, dyslipidaemia and hypertension (but not obesity). There is evidence that both antenatal and post natal factors may contribute to MS causation in a paradigm where the antenatal environment *predisposes* the individual to MS but it only occurs after exposure to certain postnatal triggers (Figure 2). This concept is supported by the Newcastle Thousand Families Study which reported how fetal life explained 2% of plasma glucose variation in 50 year olds whilst adult lifestyle and weight explained 8–13% variation.

Antenatal mechanisms

The first report associating reduced birth weight and components of MS was published in 1992 and focussed on insulin resistance and lead to the "thrifty phenotype" hypothesis, which proposes that: "poor fetal and infant growth and the subsequent development of type 2 diabetes and the metabolic syndrome result from the effects of poor nutrition in early life, which produces permanent changes in glucose-insulin metabolism". The results of many other studies, whose results have been collated in systematic review and meta-analysis, have associated reduced birth weight with hypertension and, to a lesser extent, dyslipidaemia. Increased birth weight is consistently a risk factor for childhood obesity. Birth weight is the end point of pregnancy and until recently, what remained unknown was when the association between altered fetal growth and MS outcomes is first

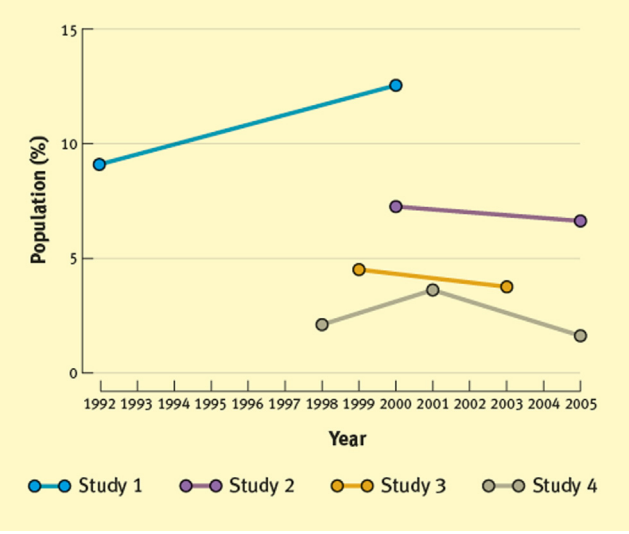

Figure 1 Prevalence of metabolic syndrome over time in four studies where the same criteria were applied in more than one cross sectional survey of a population.