

Body Mass Index From Early to Late Childhood and Cardiometabolic Measurements at 11 to 12 Years

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abstract

OBJECTIVES: To examine how overweight and obesity at specific ages and overall BMI growth patterns throughout childhood predict cardiometabolic phenotypes at 11 to 12 years.

METHODS: In a population-based sample of 5107 infants, BMI was measured every 2 years between ages 2 to 3 and 10 to 11 years. We identified 5 BMI trajectories using growth curve models. At ages 11 to 12 years, 1811 children completed assessments for metabolic syndrome risk scores, carotid-femoral pulse wave velocity, and carotid intima-media thickness. Multivariable regression models were used to estimate associations, adjusted for potential confounders (eg, age, sex, smoking exposure, and small for gestational age).

RESULTS: Overweight and obesity from early childhood onward were strongly associated with higher cardiometabolic risk at 11 to 12 years of age. At age 6 to 7 years, compared with those with a healthy weight, children with overweight had higher metabolic syndrome risk scores by 0.23 SD units (95% confidence interval 0.05 to 0.41) and with obesity by 0.76 SD units (0.51–1.01), with associations almost doubling by age 10 to 11 years. Obese (but not overweight) children had higher outcome pulse wave velocity (0.64–0.73 SD units) from ages 6 to 7 years and slightly higher outcome carotid intima-media thickness (0.20–0.30 SD units) at all ages. Cumulative exposure to high BMI from 2 to 3 years of age carried the greatest cardiometabolic risk, with a gradient of risk across trajectories.

CONCLUSIONS: High early-childhood BMI is already silently associated with the development of cardiometabolic risk by 11 to 12 years, highlighting the urgent need for effective action to reduce overweight and obesity in early childhood.



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WHAT'S KNOWN ON THIS SUBJECT: Researchers evaluating the effects of early-life BMI on cardiometabolic health tend to focus on a single measurement of childhood BMI and adult outcomes. Knowing when and how early-life BMI impacts cardiometabolic phenotypes in childhood could guide prevention efforts.

WHAT THIS STUDY ADDS: By examining overweight and obesity at 5 time points and overall BMI growth patterns throughout childhood, we show that early-life overweight and obesity and high BMI growth patterns are already silently associated with the development of cardiometabolic risk at 11 to 12 years.

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The obesity pandemic is a public health priority.¹ It threatens to undermine progress toward the decline in cardiovascular mortality in high-income countries, largely achieved through preventive efforts focused on cardiovascular risk factors.² Cardiovascular disease often arises from atherosclerosis, a pathophysiologic process that has its origins in early life.³ Childhood obesity is consistently one of the strongest predictors of obesity and cardiovascular disease in adulthood.²⁻⁴ In addition, associations of childhood overweight and obesity with subsequent metabolic disease and subclinical markers of atherosclerosis in adulthood can be explained by the strong tracking of BMI from childhood to adulthood.^{4,5}

Researchers evaluating the effects of early-life BMI on cardiovascular and metabolic (cardiometabolic) disease have mainly had only a single measurement of childhood BMI and focused on adult cardiometabolic outcomes.^{4,6} This overlooks the considerable physiologic changes in BMI throughout childhood as part of typical growth. Specific patterns of BMI may incur additional cardiometabolic risk. For example, accelerated BMI growth during the preschool years can be used to predict sustained obesity in adolescence.⁷ In addition, an early age at BMI rebound has been associated with a higher metabolic risk in early adolescence.⁸ To date, no studies have used serial data across several time points to examine the extent to which timing and/or growth trajectories influence preclinical cardiovascular phenotypes of function and structure in later childhood. This is of potential importance if BMI at certain ages or patterns over time is particularly sensitive for later cardiometabolic risk.

We therefore aimed to determine the extent to which (1) BMI at 5 time

points and (2) BMI trajectories from 2 to 3 years of age can be used to predict preclinical cardiometabolic phenotypes at ages 11 to 12 years.

METHODS

Study Design and Participants

Data are derived from the Longitudinal Study of Australian Children (LSAC) birth cohort and its cross-sectional biomarkers and physical assessment module, the Child Health CheckPoint (CheckPoint). Detailed methodology is described elsewhere.^{9,10} Briefly, in 2004, LSAC recruited a nationally representative birth cohort of 5107 infants at ages 0 to 1 years using a 2-stage random sampling design from Australia's universal health care system. Data have been collected at home visits every 2 years since 2004. CheckPoint took place between the LSAC's sixth and seventh wave of data collection. At wave 6 (ages 10–11 years in 2014), the 3764 retained families were invited to consent to their contact details being shared with CheckPoint.⁹ Consenting families were then contacted; ultimately, a total of 1874 (50% of LSAC wave 6) children participated in CheckPoint, and 97% ($n = 1811$) of these children had early-life BMI and ≥ 1 cardiometabolic health measure available (Supplemental Fig 4).¹⁰

Informed consent was provided by a parent and/or guardian. Ethics approval was granted from the Australian Institute of Family Studies Ethics Committee (14-05) and The Royal Children's Hospital Human Research Ethics Committee (33225).

Procedure

CheckPoint assessments took place between February 2015 and March 2016 for the children and parents at child ages 11 to 12 years. Most families attended 1 of 15 assessment centers across Australia, where a wide range of physical and biomarker measures were

administered with a strong focus on cardiometabolic health. Those unable to attend were offered a shorter home visit, which did not offer venipuncture or carotid intima-media thickness (cIMT).

Measures

To record biennial BMI from ages 2 to 3 to 10 to 11 years, children's height and weight (nearest 0.1 cm and 0.1 kg, respectively) were measured using standard anthropometric equipment (children did not wear shoes and were in light clothing). Height was measured 2 times and a third time if the first 2 measurements differed by >0.5 cm; the mean of both or all measurements was used. At each time point, BMI was converted to age- and sex-specific BMI z scores by using the US Centers for Disease Control and Prevention (CDC) growth reference values and to 4 categories of BMI status (underweight [<5 th percentile], healthy weight [≥ 5 th percentile and <85 th percentile], overweight [≥ 85 th and <95 th percentile], and obesity [≥ 95 th percentile]).¹¹ The underweight and healthy weight categories were subsequently combined given the small number of underweight children who were likely to have favorable cardiovascular function or structure (later confirmed). Thus, this group is referred to as the "healthy" weight category.

Cardiometabolic Phenotypes at Ages 11 to 12 Years

Metabolic Syndrome Risk Score

We calculated a continuous metabolic syndrome (MetS) risk score using 4 of the 5 traditional components of adult MetS: systolic blood pressure, high-density lipoprotein (HDL) cholesterol, triglycerides, and glucose. This MetS risk score was generated without BMI to ensure our regression analyses did not contain child BMI as both an exposure and outcome. It was derived by using principal components

analysis (varimax rotation) and is henceforth referred to as the “MetS risk score.”¹² This involved generating an age- and sex-specific z score for each of the 4 MetS risk components. We then ran the principal components analysis, which identified 2 principal components that were summed, with weights determined by the relative amount of variance explained to generate a total MetS risk score. This method has been used previously in pediatric populations, with a 1 SD increase in a continuous adolescent’s MetS risk score shown to result in adults with a 30% to 78% increased risk of type 2 diabetes and a 12% to 61% increased risk of high cIMT.¹³

We also calculated a traditional continuous MetS risk score, including BMI, for comparison to previous studies. This score included all 5 components of adult MetS: BMI z score, systolic blood pressure, HDL cholesterol, triglycerides, and glucose. The NHANES (12–19-year-old participants) non-Hispanic white, sex-specific equations for male and female participants were used, which assign a weight to each measure to identify children at higher risk for developing adult diseases related to MetS. Full details are available elsewhere.¹⁴

Systolic blood pressure was assessed as the mean of 3 measurements at the right brachial artery after 7 minutes of rest in the supine position by using the SphygmoCor XCEL (AtCor Medical Pty Ltd, Sydney, New South Wales, Australia).

Semifasting (median of 4.2 hours postprandial, range of 50 minutes to 20 hours, and interquartile range of 3.4–4.8 hours) peripheral blood was collected, in which fasting time was calculated as the hours between last eating and/or drinking to the time of blood collection. The last time of eating and/or drinking was crosschecked against when the participant was taking part in other

CheckPoint stations (and known not to be eating). Further details of cleaning processes for the time of last eating and/or drinking can be found elsewhere.¹⁵ Semifasted bloods were processed within 4 hours at an on-site processing laboratory, with serum aliquots frozen at –80°C for batch analysis. High-throughput proton nuclear magnetic resonance spectrometry (AVANCE III 500 MHz spectrometer; Bruker Corporation, Billerica, MA) quantified serum total triglycerides, total cholesterol, HDL cholesterol, and glucose.¹⁶ Three children were identified with outlier glucose levels. Two were deemed implausible (19.0 and 16.7) and excluded, whereas the other (8.8) was deemed plausible and included.

Carotid-Femoral Pulse Wave Velocity

Pulse wave velocity (PWV) was also collected by using the SphygmoCor XCEL, as previously described.¹⁷ After a 7-minute rest, assessors obtained 1 to 3 velocity (distance divided by time) measurements while participants lay supine. In the analyses, we used the mean of all available measurements. The time component comprised simultaneously recorded carotid waveform, by using tonometric applanation, and femoral waveform, by using a cuff placed around the upper thigh inflated to subdiastolic pressure. Distance was measured with a tape measure from the carotid pulse to the suprasternal notch to the right femoral pulse to the top of the thigh cuff.

Carotid Artery Intima-Media Thickness

Common cIMT was measured via portable ultrasound (GE Vivid i BT06 with a 10-MHz L-RS vascular probe), as previously described.¹⁸ Trained researchers used real-time brightness-mode ultrasound carotid artery images with standardized protocols. Participants lay supine with their head turned 45° to the left to expose the right side of their neck.

We used a 10-MHz linear array probe (Vivid i; General Electric Healthcare, Chicago, IL) to obtain cine loops of the right common carotid artery in triplicate. A modified 3-lead electrocardiogram was used to capture cardiac cycle information concurrently.

Six raters measured cIMT using Carotid Analyzer (Medical Imaging Applications LLC, Coralville, IA) software. cIMT was measured ~10 mm proximal to the carotid bulb, over a distance of 5 to 10 mm. We reported maximum cIMT, calculated as the mean of 3 to 5 still frames, timed at the R wave by electrocardiogram, of the largest thickness measurement in this 5- to 10-mm window. For a subset of 105 images, the within-observer and between-observer coefficients of variation were 4.9% and 6.2%, respectively.¹⁸

Other Key Measures

Potential confounders known to influence both BMI and cardiometabolic phenotypes were considered, including age, sex, small for gestational age, passive smoking exposure, family socioeconomic position, and pubertal status.^{18–21}

Birth weight and gestational age from wave 1 (child ages 0–1 years) were used to calculate “small for gestational age,” defined as <10th percentile according to Australian norms.²²

Questionnaire data were used to assess if the child was “ever exposed to passive smoke” and considered positive if the parent reported a smoker(s) living in the home in any LSAC wave. Family socioeconomic position at LSAC wave 6 (ages 10–11 years) is a composite measure combining parent-reported combined household income, “prestige” of the current or most recent occupation of each parent, and the highest educational qualification of each parent.¹⁸ The unweighted average

score of these items at each wave was then standardized to have a mean of 0 and SD of 1, which can be interpreted like a z score. Children self-reported on their pubertal status at CheckPoint using the 5-item Pubertal Development Scale,²³ which was categorized as pre-, mid-, or late or postpubertal.

Other CheckPoint assessment measures considered in analyses were systolic blood pressure (described above) and low-density lipoprotein (LDL) cholesterol, derived from the same nuclear magnetic resonance pass as the other biomarkers above.

Statistical Analysis

As previously published,²⁴ to examine trajectories of BMI z scores across 5 waves (LSAC waves 2–6: ages 2–3 to 10–11 years), we conducted group-based growth curve trajectory modeling using the Stata (Stata Corp, College Station, TX) traj plug-in.²⁵ All LSAC children with height and weight data available for ≥ 4 waves were used to generate BMI z score trajectories ($n = 3900$) fitted to a censored normal distribution. To identify meaningful trajectories, we considered Bayesian information criterion values, average posterior probabilities, the proportion of the sample in each trajectory, and visual graphs of trajectories. Nonsignificant (ie, $P > .05$) quadratic or cubic parameters for each trajectory were dropped (Supplemental Tables 3 and 4). This method was used to identify 5 trajectories (Fig 1), which we named “low” (6.6%), “healthy” (29.5%), “low to high” (6.0%), “always high” (42.9%), and “always very high” (15.0%). All but the low-to-high trajectory were relatively flat throughout childhood.

Univariable and multivariable linear regression models were used. The reference group for time-point analyses comprised children with healthy weight at each wave. For trajectory analyses, the reference

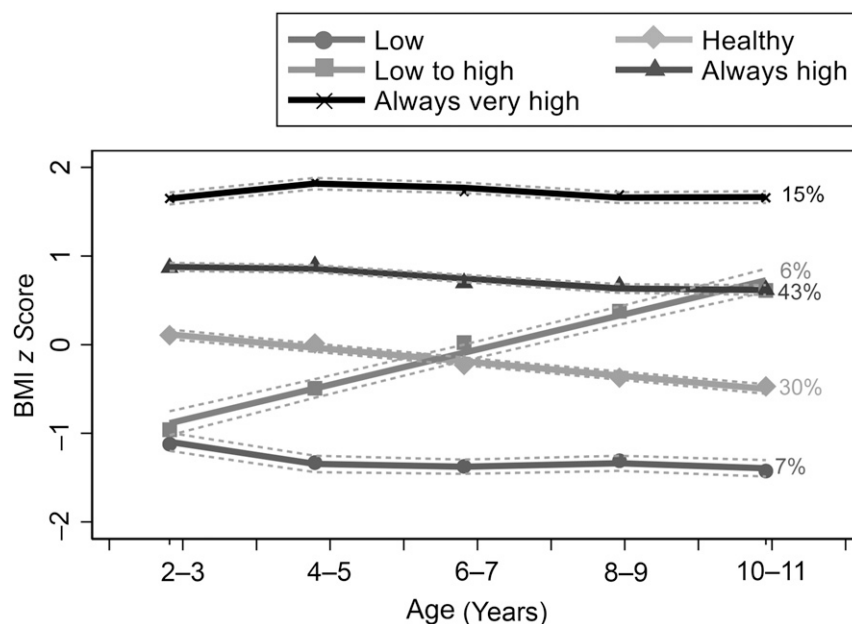


FIGURE 1

BMI z scores trajectories during childhood. BMI z score (CDC) trajectories were created by using growth curve models, from ages 2 to 3 years to ages 10 to 11 years, in which broken lines represent 95% CIs.

group comprised children following the low BMI trajectory, which was selected because it contained enough children to make meaningful comparisons and was likely to have the best cardiometabolic health (later confirmed). We internally standardized cardiometabolic outcomes to have a mean of 0 and SD of 1 so that regression coefficients represented the standardized mean difference (SMD) compared with the reference group. The amount of variance explained by the BMI status and BMI trajectories was estimated by using the coefficient of determination (ie, R^2). In addition, we dichotomized each preclinical cardiometabolic phenotype to examine the relative risk of being equal to or above the internal 75th percentile (ie, in the quartile with the highest risk) via modified Poisson regression models.²⁶

Three sensitivity analyses were also conducted, firstly for PWV and cIMT, to consider the potential effects of LDL cholesterol and systolic blood pressure, because they could lie on

the causal pathway between the BMI and cardiometabolic phenotypes. Secondly, we also ran a sensitivity analysis using CheckPoint sample (survey) weights in our analyses using Stata survey techniques to address missing data. Finally, we considered the associations for BMI status and trajectories with MetS risk score including BMI to see whether results were in the anticipated direction.

RESULTS

Sample characteristics are shown in Table 1. Our analytic sample (51% boys; mean age of 11.5 [SD of 0.5] years) had similar rates of childhood overweight and/or obesity to the Australian population.²⁷ On average, children came from slightly more socioeconomically advantaged households than the average LSAC wave 6 household (socioeconomic position of 0.18 [SD of 0.99] vs 0.00 [SD of 1.0]). Children’s mothers were predominantly born in Australia or the United Kingdom (71%).

TABLE 1 Sample Characteristics

Child Characteristics	N = 1811
Male sex, %	51
Mother's country of birth, %	
Australia	60
United Kingdom	11
Other	29
Aboriginal and/or Torres Strait Islander, %	2
Birth wt, kg, mean (SD)	3.4 (0.6)
Small for gestational age, %	9
Wave 6 (10–11 y old)	
Socioeconomic position, z score, mean (SD)	0.18 (0.99)
Ever exposed to passive smoke in home, %	16
CheckPoint (11–12 y old)	
Age, y, mean (SD)	11.5 (0.5)
Pubertal stage, ^a %	
Prepubertal	10
Early to midpubertal	77
Late to postpubertal	13
BMI z score (CDC), mean (SD)	0.32 (0.98)
BMI status (CDC cut points), %	
Overweight	15
Obese	9
Cardiovascular function, mean (SD)	
Systolic blood pressure, mm Hg	108.1 (8.0)
Diastolic blood pressure, mm Hg	62.4 (5.7)
MetS risk score ^b	−0.00 (1.02)
MetS risk score including BMI z score ^c	−0.18 (0.69)
PWV, m/s	4.46 (0.57)
Cardiovascular structure, cIMT, mm, mean (SD)	0.58 (0.05)

^a Self-reported pubertal status was assessed by using the 5-item Pubertal Development Scale.

^b The MetS risk score included systolic blood pressure, HDL cholesterol, triglycerides, and glucose and was derived by using principal components analysis (varimax rotation).

^c The MetS score including BMI z score was derived by using the continuous algorithm on the basis of US data for 12- to 19-y-old participants from the US NHANES.

Early-Life Overweight and Obesity at 5 Time Points and Cardiometabolic Health at 11 to 12 Years

In univariable analysis (data not shown), the amount of variance explained by overweight and obesity (ie, R^2) typically increased with age for cardiometabolic outcomes. The MetS risk score variance explained was 1% for BMI at ages 2 to 3 and rose to 11% for BMI at 10 to 11 years. Values for PWV rose similarly from 1% to 4%, whereas variance explained for cIMT was consistently 1%. Potential confounders helped explain the variance in cardiometabolic phenotypes (Supplemental Table 5).

In multivariable models (Fig 2), from ages 6 to 7 years, children with overweight had a higher MetS risk

score at age 11 to 12 years. For example, at 6 to 7 years those with overweight had a higher MetS risk score by 0.23 SD units (95% confidence interval [CI] 0.05 to 0.41), and those with obesity had a higher MetS risk score by 0.76 SD units (95% CI 0.51 to 1.01), compared to children with healthy weight. These associations almost doubled by ages 10 to 11 years. Children with obesity (but not overweight) from 6 to 7 years had a higher outcome PWV (0.64–0.73 SD units), whereas they had slightly higher outcome cIMT across all age groups (0.20–0.30 SD units).

When cardiometabolic outcomes were dichotomized, similar patterns emerged across time points (Supplemental Fig 5).

Early-Life BMI Trajectories and Their Relationship With Cardiometabolic Health

For BMI trajectories, univariable and multivariable estimates were similar in magnitude (Table 2). In univariable analyses, BMI trajectory accounted for <1% of the variance in cardiometabolic outcomes. In multivariable regression models, compared with children following the low BMI trajectory, other trajectory groups had higher levels of MetS risk score at 11 to 12 years, ranging from an SMD of 0.46 to 0.92. PWV was also higher in children following other (except the healthy) trajectories, whereas differences in cIMT were less pronounced.

Overall, compared with the low-trajectory group, those in the always-very-high group had the poorest cardiometabolic health, with higher MetS risk scores (SMD of 0.92 [95% CI 0.63 to 1.25]; PWV of 0.68 [95% CI 0.45 to 0.91]) and moderately higher cIMT (0.47 [95% CI 0.21 to 0.74]).

When cardiometabolic outcomes were dichotomized, results were similar (Fig 3), revealing a markedly higher cardiometabolic risk for children who followed the always-very-high trajectory.

All results were similar when cIMT and PWV analyses were additionally adjusted for LDL cholesterol and systolic blood pressure (data not shown). Similar results were also found when applying survey weights (data not shown). Effect estimates were larger for MetS risk score including BMI (Supplemental Fig 6) compared to our MetS risk score excluding BMI, which is reported in our main results.

DISCUSSION

Principal Findings

Childhood overweight and obesity from early childhood are associated with a higher MetS risk score, higher arterial stiffness, and increased cIMT

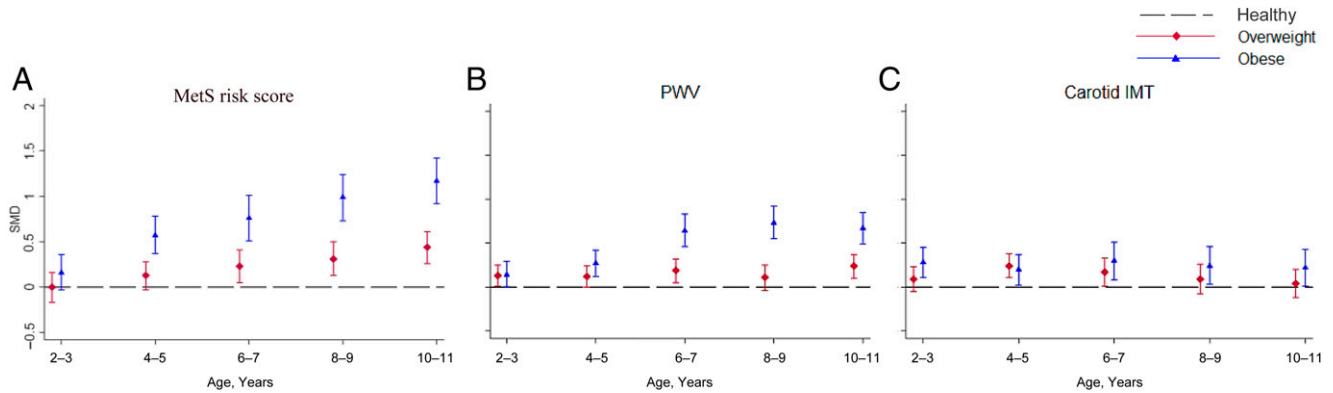


FIGURE 2

Cardiometabolic risk at each time point for children with overweight or obesity compared with those who are healthy weight. SMDs, with 95% CIs, in cardiometabolic health at age 11 to 12 years in children with overweight and obesity are compared with those in children with healthy weight at 5 earlier ages. Linear regression estimates are adjusted for socioeconomic position, sex, age, puberty status, passive smoke exposure, and born small for gestational age. A, MetS risk score. B, PWV. C, cIMT.

at ages 11 to 12 years. When looking at BMI at the 5 biennial time points separately (ie, ages 2–3 to 10–11 years), associations with cardiometabolic scores at 11 to 12 years strengthened with age. Growth trajectory analyses revealed that cumulative exposure to high BMI carried the greatest cardiometabolic risk and revealed a gradient of risk across the series of BMI trajectories.

Previous studies examining BMI and cardiometabolic health have tended to rely on a single BMI time point in childhood and focused on cardiometabolic outcomes in

adulthood.^{2–4} Through our findings, we extend these studies by measuring BMI over time and cardiometabolic phenotypes in midchildhood. Our results are in keeping with previous studies but provide additional important insights that suggest BMI from as early as 2 to 3 years of age is predictive of preclinical cardiometabolic phenotypes by ages 11 to 12 years.

Authors of several studies have evaluated the trajectory patterns of childhood BMI,^{8,28–32} with typically 3 to 4 distinct trajectories being defined. Most individuals follow

a relatively stable trajectory throughout childhood compared with their peers. Higher BMI trajectories have previously been associated with a higher fasting insulin concentration at age 14 years³³ and higher blood pressure values at age 18 years, as well as obesity, increased cIMT, and left ventricular mass in adulthood.^{28,31,32} In line with these studies, BMI trajectories in our sample were relatively stable, and a consistently high BMI trajectory was associated with worse cardiometabolic phenotypes at 11 to 12 years of age. Given that

TABLE 2 Differences in Mean Cardiometabolic Health Measures at 11–12 Years by 4 BMI z Score Trajectory Groups From 2–3 to 10–11 Years of Age Compared With Those in the Low Trajectory (Reference Group)

BMI z Score Trajectories	MetS Risk Score		PWV		cIMT	
	SMD (95% CI)	P	SMD (95% CI)	P	SMD (95% CI)	P
Unadjusted estimates						
Model R^2 , %	0.7		0.4		0.2	
Low (reference group)	—		—		—	
Healthy	0.12 (–0.14 to 0.38)	.38	0.14 (–0.06 to 0.34)	.18	0.08 (–0.15 to 0.31)	.51
Low to high	0.46 (0.09 to 0.82)	.02	0.41 (0.14 to 0.69)	.003	0.21 (–0.10 to 0.51)	.19
High	0.41 (0.15 to 0.66)	.002	0.18 (–0.01 to 0.38)	.07	0.31 (0.08 to 0.53)	.008
Always very high	0.99 (0.70 to 1.29)	<.001	0.74 (0.51 to 0.96)	<.001	0.48 (0.23 to 0.74)	<.001
Adjusted estimates						
Model R^2 , %	.9		.7		.4	
Low (reference group)	—		—		—	
Healthy	0.21 (–0.07 to 0.47)	.14	0.16 (–0.39 to 0.37)	.11	0.10 (–0.14 to 0.33)	.42
Low to high	0.46 (0.08 to 0.83)	.02	0.44 (0.16 to 0.72)	.002	0.28 (–0.04 to 0.60)	.09
High	0.42 (0.16 to 0.68)	.001	0.20 (0.00 to 0.40)	.04	0.28 (0.09 to 0.55)	.007
Always very high	0.92 (0.62 to 1.23)	<.001	0.68 (0.45 to 0.91)	<.001	0.47 (0.21 to 0.74)	.001

MetS risk score included systolic blood pressure, HDL cholesterol, triglycerides, and glucose. The BMI z score is the BMI standardized for age and sex (CDC growth charts). R^2 is the amount of variance the exposure(s) explain in each outcome. —, not applicable.

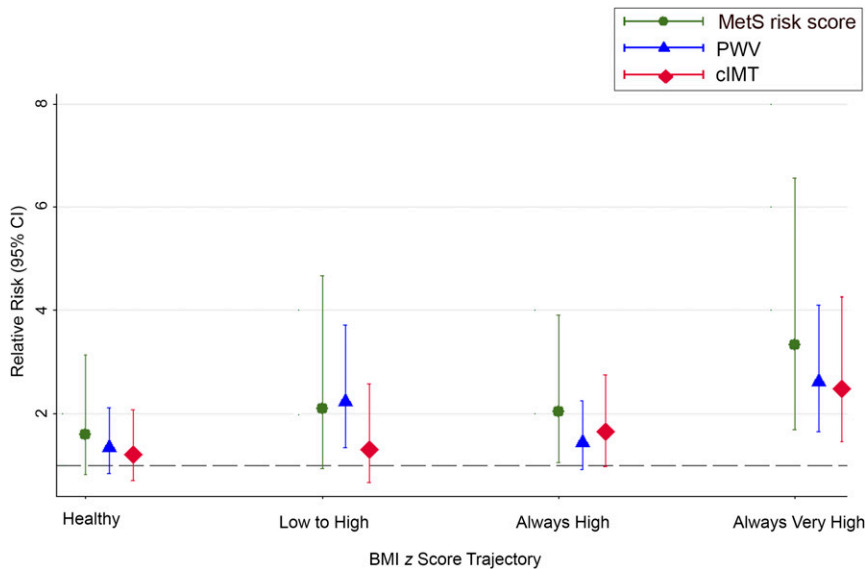


FIGURE 3

Relative risk of poor cardiometabolic health at age 11 to 12 years for BMI z score trajectories compared with the low trajectory. The relative risk of being >75th percentile on each preclinical cardiometabolic phenotype at age 11 to 12, by BMI z score trajectories, in which the reference category is the low trajectory, is shown. All estimates of relative risk were adjusted for socioeconomic position, sex, age, puberty status, passive smoke exposure, and born small for gestational age.

trajectories were relatively stable over time and cardiometabolic phenotypes were only measured at one time point, it is possible that our longitudinal associations reflect associations that emerge in midchildhood. To establish exactly when these associations emerge requires repeated measures of both BMI and cardiometabolic phenotypes throughout childhood.

From a clinical perspective, our data suggest that BMI from 2 to 3 years onward is generally relatively stable among the majority of children and is associated with subsequent preclinical cardiometabolic phenotypes. In terms of intervention efforts that are focused on childhood obesity, our data provide unique evidence that early-life BMI measurements predict cardiometabolic risk later in childhood. The magnitude of associations is also likely to translate into clinically important differences for children in the consistently high BMI trajectories. Compared with

children in the low trajectory, those in the always-very-high trajectory had close to a 1 SD high MetS risk score (SMD of 0.92 [95% CI 0.62 to 1.23]). In one of our previous studies,¹⁴ a 1 SD higher continuous MetS risk score was associated with an elevated risk of type 2 diabetes and higher cIMT in adulthood, highlighting the clinical significance.

When we dichotomized cardiometabolic health measures, the adverse associations with consistently high BMI were also marked. Growth patterns have been associated with differential cardiometabolic risk by early adolescence, with children with a normal peak-early rebound pattern or without any BMI decline after infancy having higher insulin resistance and metabolic risk scores.⁸ Because our methodologic approach was used to generate summary BMI trajectory patterns and was designed to reveal empirical “typical” groupings of patterns rather than individuals with early adiposity

rebound, our findings are not directly comparable. Notwithstanding, we observed effects early in life when BMI was considered across the 5 biennial time points separately. Infant BMI was not included because length was not collected in LSAC wave 1. However, when we adjusted estimates for small for gestational age, the results were essentially unchanged.

Despite the strong associations we observed between groups, the amount of variance in cardiometabolic phenotypes explained (R^2) was relatively small for both the time-point and trajectory analyses. However, at the population level, the small amount of variance explained is still likely to be meaningful, and this is likely to increase as the pathogenesis of cardiometabolic disease develops over the life course with cumulative risk factor exposure.

Our findings have public health implications because they highlight the subclinical effects of obesity in childhood. This highlights the importance of early interventions when trajectories are likely to be more malleable and adverse cardiometabolic phenotypes are reversible.⁴ The 2017 World Health Organization Commission on Ending Childhood Obesity report argued that multisectoral action is urgently needed to address the obesogenic environment.³⁴ Such action requires systems-based approaches and policy implementation. Until this is realized, we must continue to try to curb the obesity pandemic at all levels (eg, family, child care, and school) throughout childhood to promote healthy weight and healthy eating, sleep, screen, and activity behaviors in the hope of setting healthy weight trajectories in childhood that track into adolescence and adulthood.³⁵

Limitations

The study cohort is not completely population representative. Compared

with the original population-based sample ($n = 5107$), those who did not take part ($n = 3233$) were largely comparable to CheckPoint participants ($n = 1874$) at baseline (ie, 2004). The exception was that compared with CheckPoint families, those lost to follow-up came from more socioeconomically disadvantaged families (baseline Socio-Economic Indexes for Areas mean of 1019 [SD of 61] vs 1003 [SD of 59]), were more likely to be of indigenous background (2% vs 6%) and have parents whose home language was not English (11% vs 16%).¹⁰ However, after applying survey weights, which accounted for nonresponse and loss to follow-up over the 6 waves of the LSAC from 2004 to 2015, the associations were largely unchanged.

Because of the young age of the study population (11–12 years), it is not possible to evaluate the effects of BMI on actual cardiovascular disease or events. Instead, their cardiometabolic health was evaluated by using preclinical phenotypes (MetS risk scores, cIMT, and PWV) known to be associated with conventional cardiovascular risk factors in adulthood and used to predict overall cardiovascular morbidity.^{36–38}

Physical activity and dietary intake both reveal complex relationships with BMI and cardiometabolic health. We chose not to treat them as potential confounders in these analyses for several reasons: (1) neither could be adequately measured at or before baseline, (2) our previous work in this cohort has revealed that an inflammatory diet is not related to cardiovascular function and structure in children,³⁹ and (3) in crosslagged wave-on-wave analyses, dietary scores and/or patterns did not consistently predict weight-to-height ratio and BMI z score or vice versa in subsequent waves.⁴⁰ Finally, blood samples were collected after a semifast (median time of 4.2 hours) rather than a traditional 8-hour fast. However, previous data suggest that a random sampling or fasting for a 3-hour period is sufficient for reliable glucose measurements,⁴¹ and current guidelines recommend that nonfasting blood samples can be routinely used for the assessment of plasma lipid profiles.⁴²

CONCLUSIONS

BMI from 2 to 3 years of age onward is associated with MetS risk and subclinical markers of atherosclerosis

by 11 to 12 years. These findings suggest that public health efforts are needed in early childhood to mitigate overweight and obesity to avoid associated cardiometabolic risks that are already emerging in childhood.

ACKNOWLEDGMENTS

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ABBREVIATIONS

CDC: Centers for Disease Control and Prevention
CI: confidence interval
cIMT: carotid intima-media thickness
HDL: high-density lipoprotein
LDL: low-density lipoprotein
LSAC: Longitudinal Study of Australian Children
MetS: metabolic syndrome
PWV: pulse wave velocity
SMD: standardized mean difference

Dr Lycett and Prof Juonala led this work, made substantial contributions to the design of the study, analysis of the data, and interpretation of data, drafted the article, and revised it critically on the basis of coauthor feedback; Dr Magnussen and Mr Norrish contributed to statistical analyses, particularly the creation of metabolic syndrome risk scores and BMI trajectories, respectively, contributed to the interpretation of data, and revised the article critically for important intellectual content; Dr Mensah is an investigator on the Child Health CheckPoint study and made substantial contributions to the design of the study, oversaw all data analyses and interpretation of data, and revised the article critically for important intellectual content; Profs Carlin, Olds, Saffery, Ranganathan, Baur, Sabin, Cheung, and Dwyer and Dr Kerr are investigators on the Child Health CheckPoint study and contributed to the study design and interpretation of data and revised the article critically for important intellectual content; Drs Clifford and Liu and Ms Liu made substantial contributions to the conception and design of the study and interpretation of data and revised the article critically for important intellectual content; Profs Wake and Burgner supervised this work within Dr Lycett's fellowship and are chief investigators of the Child Health CheckPoint study, made substantial contributions to the conception and design of the study and interpretation of data, and revised the article critically for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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