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Pediatric Congenital Heart Disease (G Singh, Section Editor)

Childhood Obesity, Arterial Stiffness, and Prevalence and Treatment of Hypertension

Kathryn R. Armstrong, MD[1]
Anita T. Cote, PhD[2]
Angela M. Devlin, PhD[2]
Kevin C. Harris, MD, MHSc[1,2,*]

Address
*,[1]Division of Cardiology, BC Children's Hospital, Children's Heart Centre, 1F–4480 Oak Street, Vancouver, BC V6H 3 V4, Canada
Email: kharris2@cw.bc.ca
[2]Department of Pediatrics, University of British Columbia, Child and Family Research Institute, Vancouver, BC, Canada

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Kathryn R. Armstrong and Anita T. Cote: Authors contributed equally.
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Opinion statement

Childhood obesity is associated with progressive vascular dysfunction as manifest by arterial stiffness and elevated blood pressure with associated subsequent morbidity and mortality because of early cardiovascular events including myocardial infarction and stroke in adulthood. Consequently, the recent dramatic increases in childhood obesity around the world present a hitherto unforeseen public health concern. While coordinated primary prevention efforts remain an ongoing important focus of action, identification and treatment of modifiable cardiovascular risk factors in pediatric patients is necessary given the existing burden of disease and future health consequences. Lifestyle interventions remain a cornerstone of our therapeutic approach, however, medical therapy is needed in some cases and should not be underutilized based on patient age. Herein, we discuss the relationship between childhood obesity and hypertension with a key emphasis on the

evolution of adaptive and maladaptive vascular changes in the genesis of overt cardiovascular disease.

Introduction

The relationship between childhood obesity and hypertension is well described [1] with the prevalence of hypertension increasing progressively with increasing body mass index (BMI) [2]. The incidence of childhood obesity is reported to have increased from 5 % to 11 % through the 1960s to the 1990s [2, 3] and in the latter part of the 2000s, while the prevalence of obesity in the United States is estimated to be 18 % among school aged children and 18.4 % in adolescents [4]. Obesity in childhood has become a problem of epidemic proportions and is associated with cardiovascular disease in both children and adults [5•].

Hypertension is a major risk factor for cardiovascular morbidity and mortality. In children, hypertension is defined as systolic (SBP) and/or diastolic blood pressure (DBP) ≥95th percentile for sex, age, and height, while prehypertension is blood pressure (BP) within the 90th–95th percentiles [6]. Hypertension is a modifiable risk factor for the development of cardiovascular disease and is one of the leading causes of morbidity and mortality worldwide [7–9]. It is concerning, but not surprising, that the global prevalence of elevated BP in children is on the rise [10, 11] concurrent with the rise in childhood obesity [12, 13]. Current estimates of rates of hypertension in childhood range from 7 % to 17 % worldwide [14]. In the United States, the National Health and Nutrition Examination Survey (NHANES) results from 1988–1994 found the prevalence of hypertension to be 15.8 % in boys and 8.2 % in girls [15]. The same study group from 1999–2008 found that the prevalence of hypertension had increased to 19.2 % in boys and 12.6 % in girls. Notably, reported rates of the prevalence of pediatric hypertension are often considered underestimates as many children go undiagnosed [16]. The surveillance coordinated in the NHANES data collection is intended to provide a representation of the broad American population, which is a particular strength of that data set.

Elevated BP in childhood often tracks into adulthood and is associated with hypertension later in life [17, 18]. In adults, aortic stiffness is associated with future incident hypertension [19], promoting the assessment of arterial stiffness as a tool for early detection and prevention. This review will focus on the symbiotic relationship of arterial stiffness and hypertension in childhood obesity.

Epidemiology of elevated BP in childhood obesity

The increasing prevalence of hypertension in children appears to be strongly tied to the burgeoning prevalence of childhood obesity. This association has been demonstrated in numerous epidemiologic studies across the globe [20–22]. A recent large population-based study of American children reported an increased prevalence of elevated BP over a 20-year period, a linear relationship between BMI and BP, and greater odds of elevated BP for children in the upper compared with lower categories of BMI [10]. Obesity is independently associated with both prehypertension and hypertension [15]. In children with obesity, the risk of hypertension is reported to be approximately threefold higher than the risk in nonobese children [2]. Even high normal BP in childhood is associated with the development of hypertension [17] and signs of very early target-organ damage, such as ventricular hypertrophy and arterial wall thickening, in young adulthood [23, 24]. Thus, the increased prev-

alence of obesity and elevated BP in childhood, independently and collectively contribute to augmenting risk of cardiovascular morbidity and mortality and are now a global health concern.

Epidemiology of arterial stiffness in childhood obesity

Childhood obesity is associated with adverse vascular changes in adulthood [25, 26]. Indicators of atherosclerotic development such as increased intima media thickness (IMT) and arterial plaque, appear to be distinct in pathology from arteriosclerotic developments such as aortic stiffness [27], the later thought to manifest first [28]. Recently, similar changes have been documented in obese children. Whereas reports of augmented IMT and/or plaque load in children is less common, there is mounting evidence of arterial stiffness in obese children [29]. Noninvasive assessment of arterial stiffness in children (as in adults) may involve the use of pressure-sensitive transducers, Doppler ultrasound, or applanation tonometry, aimed at measuring pulse wave velocity (PWV), arterial pressure waveforms, or relating change in vessel diameter to distending pressure, described in detail elsewhere [28, 30–32]. A recent meta-analysis involving 15,877 adult participants from 17 studies, followed for a mean of 7.7 years, deemed aortic pulse wave velocity, considered the gold standard for measuring arterial stiffness, to be a significant predictor of cardiovascular events and all-cause mortality [33••]. Consequently, the finding of increased aortic pulse wave velocity in children is particularly ominous [34–41]. Arterial stiffness has a higher predictive ability for future cardiovascular events in adults with higher baseline cardiovascular risk [33••]. Thus, while the long-term prognosis of arterial stiffness in childhood on future risk is currently not known, these findings suggest children with obesity may benefit from early assessment, particularly given the likelihood of elevated BP and other comorbidities these children may possess.

The assessment of arterial stiffness in children with obesity has mainly been a research focus in the last 10 years. The majority of studies have reported children and adolescents with obesity have higher aortic PWV [34–41] and increased aortic or carotid beta index [34, 35, 41–45]. Using a different research design, Sakuragi et al. [46•] compared arterial stiffness across three tertiles of body fat, determined by Dual-energy X-ray absorptiometry, in community-based sample of 573 children. These researchers reported higher PWV relative to body fat. They also demonstrated a negative relationship between PWV and cardiorespiratory fitness. In contrast, one investigation reported PWV was not correlated with obesity index [47], and three others found PWV was lower in obese children [48–50]. Discrepancies may be partly explained by different methods used to assess PWV such as brachial-ankle [47] and carotid-radial [48], which involve peripheral segments of the arterial tree. Evidence of increased artery diameter and systemic blood flow in obese children [50] imply that initially these children are showing physiological adaptation to the increased growth, albeit excess adiposity, much like that which occurs during normal growth and development. It is not clear at what point these changes progress to a maladaptive disease process. In support of this concept, Dangardt and colleagues performed a follow-up study [51•]. While initially children with obesity (mean age, 13.9 ± 1.6 years)

displayed lower carotid-radial PWV, 5 years later in late adolescence, arterial stiffness was increased 23 % in these children, compared with a 3 % increase in the lean controls. Interestingly, these researchers also found that the increase in PWV and DBP was associated with the baseline BMI z-score of these children. Thus, collectively, the research indicates that childhood obesity impacts negatively on vascular adaptation, although when and how this maladaptation evolves remains an important area of ongoing investigation.

Pathophysiology of elevated BP and arterial stiffness in children with obesity

Arterial stiffness progressively increases with age as elastin fibers of the arterial wall fatigue and fracture due to mechanical stress [52]. While the direct relationship between arterial stiffness and hypertension are not fully understood, more evidence of arterial stiffening, in advance of that observed with normal aging, as a precursor to hypertension is becoming apparent [19, 53–55]. In childhood obesity, the development of arterial stiffening is likely dependent on environmental and genetic factors unique to each child and is difficult to ascertain in the absence of prospective studies. In a previous review, we proposed a theoretical interplay of mechanisms leading to cardiovascular dysfunction in children with obesity [29]. In the present review, we attempt to hone in on the mechanisms specific to arterial stiffness and how it may relate to elevated BP (Fig. 1). As the result of excess adiposity, we propose an interaction between acute structural alterations because of increased fluid volume and inflammation, which may initiate vascular remodelling involving increased collagen deposition (Fig. 1). An increased sympathetic response, also sensitive to changes in adiposity, further influences vascular tone. As obesity progresses, additional metabolic consequences of excess adipose tissue may impact vascular structure and tone [56], mediated by environmental influences and genetics [57]. Collectively, these factors increase systemic BP, which will accelerate the arterial stiffening further and potentially impair baroreflex function. In this regard, evolution of arterial stiffness and hypertension may be considered bidirectional where arterial stiffness may serve as both a risk factor for, and a risk marker of hypertension [58].

Clinical evaluation of blood pressure

Although a complete review of the clinical evaluation and treatment of pediatric hypertension is beyond the scope of this review, we have attempted to highlight current important areas of investigation and knowledge mobilization. Primary hypertension in childhood is defined as the inability to identify an underlying disease process that may cause hypertension [59]. Secondary hypertension is due to a primary disease process such as renal parenchymal or structural kidney disorders; congenital cardiac abnormalities such as coarctation of the aorta; renin mediated hypertension; and mineralocorticoid and catecholamine induced hypertension [60]. Historically, secondary hypertension was the most common

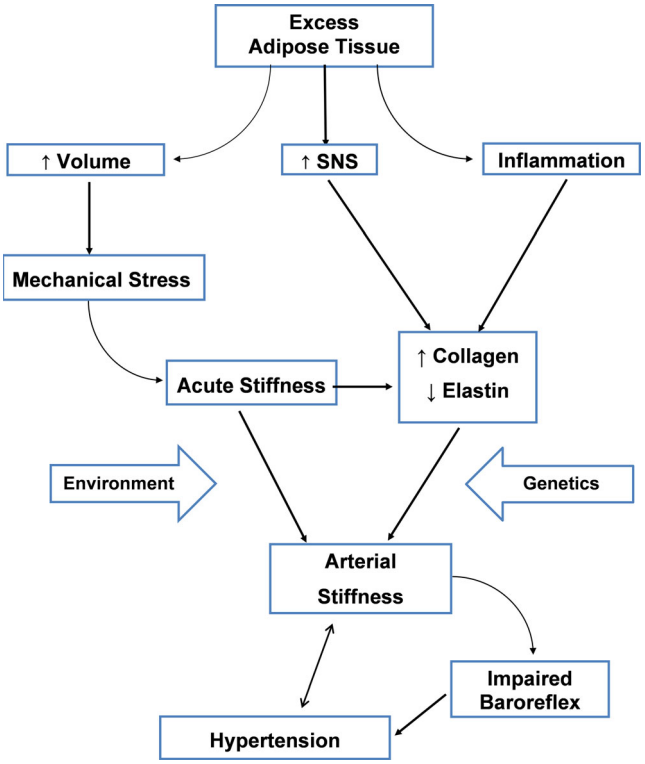

Figure 1. Proposed mechanisms linking childhood obesity to vascular changes.

form of hypertension in childhood, however, with the rising rates of childhood obesity, primary hypertension may currently be more prevalent. Risk factors for the development of hypertension in childhood in addition to obesity include family history, ethnicity, and socioeconomic status [61].

The association between elevated BP and obesity is strong, and as such routine serial measurement of BP in obese children is essential. Furthermore, increases in BMI centile are common in children. Compared with children with a BMI <50th percentile, Fields et al. found that girls and boys (8-12 years) with a BMI between the 75th and 84th percentiles were up to 20 times more likely [boys, odds ratio (OR)=4.3, P=0.02; girls, OR=20.2, P=0.001] to become overweight (BMI ≥85th centile) [62]. Boys who had a childhood BMI above the 85th percentiles were five times more likely (OR=5.1) to become hypertensive. Friedemen et al. found that the mean difference in SBP between normal weight and obese children was 40 % higher that the difference between normal and overweight children [63].

Blood pressure naturally increases with age in children as their bodies grow. The use of z-scores, accounting for age, sex, and height, reflect the deviations from expected as opposed to absolute BP [6]. For example, according to Center for Disease Control charts [64], SBP/DBP at the 50th percentile for an 11-year-old boy who is at the 5th percentile for height, would be considered normal at 99/59 mm Hg. By comparison, 116/65 mm Hg for a 16-year-old boy in the same study population, at the 50th percentile for height, would also be considered normal. However, for the 11-year-old, the latter BP would deem him prehypertensive. Even in studies involving a very narrow age range, the variability in height remains a factor that may

confound the analysis. Thus, we are unable to determine the true relationship of BP and arterial stiffness in obesity with absolute measures of BP.

While there is no clear consensus as to when to start to measure BP in children, Hoffman et al. recommended starting to track BP in children as young as 5 years of age [65], while the Fourth Report on the Diagnosis, Evaluation and Treatment of hypertension recommends measuring BP in children >3 years when they are reviewed in a medical setting [6]. Screening at a young age may allow for early complete evaluation and intervention to promote healthy weight, active lifestyle, and ongoing management of BP, which is necessary to decrease cardiovascular risk factors in children.

Risks associated with childhood obesity hypertension

Hypertension remains one of the main risk factors for the development of cardiovascular, cerebrovascular, and renal disease in adults [60]. Following diagnosis of hypertension in childhood evaluation should take place to look for the presence of end organ damage. Hypertensive patients are at risk of developing left ventricular hypertrophy (LVH), which is present in up to 40 % of children with primary hypertension [2, 23]. This LVH increases the risk for myocardial infarction and congestive cardiac failure in adults. Left ventricular mass (LVM) can be evaluated from echocardiographic measures, however in children this is confounded by the relationship between body size and heart size in the growing child. By indexing the LVM allometrically to height ($m^{2.7}$), the left ventricular mass index can be calculated (LVMI), which optimizes detection of left ventricular hypertrophy limiting errors and variation between subjects [66, 67]. However, the presence of obesity is associated with higher LVMI than is found in children with hypertension alone ($n = 4603$; $P < 0.05$). LVMI should be measured upon diagnosis of hypertension and periodically thereafter [6, 16]. The optimal threshold for determining what LVMI in childhood that is correlated with adverse health outcomes later in life has not yet been determined. A conservative cut off point to determine the presence of LVH is an LVMI of 51 $g/m^{2.7}$, which is >99th percentile for children and is associated with increased mortality in adults with hypertension [68].

Abnormalities in the renal system are a causal factor for many forms of secondary hypertension. Conversely, the prevalence of end-stage renal disease because of hypertension is well recognized, however, children do not frequently develop clinically evident renal abnormalities [13]. It is reasonable that following a diagnosis of hypertension, children should be evaluated for subclinical changes. This may include urinalysis to evaluate for microalbumuria, which is a marker of early renal damage [69], and complete renal ultrasound. Hypertensive retinopathy and impairment to cerebral vasculature may also occur in children with hypertension, and if clinical suspicion exists, these should be screened for [7].

Primary prevention

With a modifiable disease with high prevalence such as obesity-related hypertension, primary prevention is preferable to secondary prevention. For the pri-

mary practitioner, education for both children and their families is important in initiating lifestyle change. The HEALTHY primary prevention trial [70•], evaluated cardiovascular risk factors across multi-ethnic middle school pupils in the USA. Schools were randomized to a control group where no changes were made or assigned to a 2.5-year intervention program consisting of changes to school food environment and physical education classes. The intervention produced a significant decrease in both hypertension and prehypertension in non-Hispanic Black ($P=0.007$) and non-Hispanic White youth ($P=0.037$). Given that dietary habits are established in early childhood, it is important that early exposure to food should include an age-appropriate diet. The Cardiovascular Risk in Young Finns study, based on 21 years of follow-up of 3-to 18-year-old children, demonstrated that healthy dietary patterns developed in childhood continued to have a benefit with regard to cardiovascular health in adulthood [71]. The NHANES review from 2005–2010 reported that >80 % of adolescent males and females in all ethnic groups studied (non-Hispanic white, non-Hispanic black, and Mexican American) had a poor diet (based on the Healthy Diet Score, derived from the portions of fruits, vegetables, whole grains, fish, added salt, and sugar consumed on a daily basis) [72]. In a group of adolescents (n=57) with prehypertension or hypertension, Couch et al. evaluated the efficacy of a 3-month clinical-based behavioral nutrition intervention emphasizing a diet high in fruits, vegetables, and low fat dairy (DASH intervention) vs a control group who received routine outpatient hospital-based nutrition care. Those in the DASH intervention had a greater decrease in SBP*z*-score ($P<0.01$). Over the course of the study period, the children in the intervention group had a greater increase in fruit intake, potassium, and magnesium and a greater decrease in total fat compared with the control group [73].

There is overwhelming evidence to support the benefits of regular physical activity (PA), with current recommendations for healthy children to include at least one hour of moderate-to-vigorous PA (MVPA) daily with vigorous intensity, and muscle and bone strengthening activities on at least three days per week [74, 75]. Knowles et al. evaluated the cross-sectional and longitudinal associations between BP and PA, objectively measured using accelerometry, in children aged 5–7 years. Baseline total MVPA was inversely associated with DBP at both baseline [adjusted regression coefficient: −0.75 mm Hg (95 % CI −1.33 to −0.18) per 20 cpm] and follow-up [−0.74 mm Hg (95 % CI −1.40 to −0.08)], strengthening the association between higher levels of physical activity and lower BP in children as young as 5 (n=574) [76].

As children spend at least one-half of their waking day at school, school-based education and promotion of healthy lifestyle are vital. To date studies have not proven that school-based activity interventions lead to statistically significant improvements in decreasing body mass index [77, 78]. Despite this evidence, school-based physical education classes offer a prime opportunity to educate children about the benefits of healthy food choices and physical activity as part of a healthy lifestyle. The putative beneficial effects of such changes extend beyond the physical benefits to improved psychological and social wellbeing of children. If physical education in schools promoted and achieved high level activity for >1 hour up to four times/ week this could have an beneficial impact on BP at a population level. Children engaging in low sport-related physical activities at baseline but who engaged in high levels of physical activity (≥60 minutes/day) at follow-up (n=154),

compared with those engaging in low sport-related physical activities at both examinations (n=305), demonstrated significantly lower mean arterial BP (P=0.04)[79]. Even brief bouts of PA can have important health effects. In children aged 8–11 years with a family history of obesity, Saunders et al. measured the effect of sedentary behavior on BMI [80]. Those who had breaks in sedentary time and with brief sedentary bouts lasting 1–4 minutes were associated with lower BMI z-score in both sexes (P<0.05). Leisure time computer/video game use was associated with increased waist circumference in boys, while TV viewing was associated with increased waist circumference, and BMI Z-score in girls (P<0.05). The association between screen time and BP is also becoming apparent. Gopinpath et al. prospectively evaluated total screen time and its relation to BP in children over a 5-year period [79]. They concluded that each hour/day spent in TV viewing was associated with a significant increase in DBP (0.69 mm Hg) and mean arterial BP (0.59 mm Hg). Reducing screen time should remain a focus of primary prevention efforts for obesity related hypertension.

Treatment of childhood hypertension

The management of obesity related hypertension should be both multifactorial and multidisciplinary. Following diagnosis the first goal of treatment should be to promote lifestyle change which may positively impact both hypertension and obesity. While the initial step in the treatment of children with obesity and hypertension is to target weight maintenance or loss, this requires behavioral changes with regards to both dietary intake and nutrition which involve changing attitudes and education for the whole family. An example the importance of parental/family support is highlighted in a recent randomized control trial of a family-based treatment for obesity [81]. One of the main factors associated with greater weight loss and reduced SBP in children participating in this intervention (aged 8–12 years) at 6 months, was better program attendance. Through behavior interventions, families are educated in lifestyle modification that supports the health of child and family members. During the management of children with obesity it is important to remember the influence of familial factors in the development of disease and hence lifestyle recommendations should be put in context of the family situation. Unfortunately, the educational component of such programs may be best suited as a treatment for childhood obesity and its comorbidities. Evidence compiled from 26 trials (23,617 children) in a recent systematic review indicate that educational interventions are effective in treating, but not preventing, childhood obesity and accompanying elevations in DBP [82].

Exercise interventions focused on vascular outcomes in children with obesity are limited. Following six months of an exercise program, Meyer et al. [83] reported improved endothelial function and carotid intima-media thickness in children with obesity, in concert with reduced SBP, waist circumference, and biomarkers of cardiovascular risk. Similar cardiometabolic results and BP reductions were reported in an exercise intervention over a much shorter duration (10 weeks) [84]. In this study, arterial stiffness as

measured by brachial-ankle PWV did not significantly changed during this time period. It is not known whether a longer intervention would improve arterial stiffness in these children. Future studies should focus on the effectiveness of obesity treatment programs in children with, and without, hypertension, including measures of arterial stiffness to assist in our understanding of the pathology of obesity related hypertension.

In an era where social networking and social media are a common part of childhood life these modalities have recently been used to trial obesity interventions, although the results to date have been mixed [85]. Williamson et al. demonstrated that active family-based behavioral internet interventions resulted in more loss of body weight and lower dietary fat intake than passive primary health education. In comparison to the control group adolescents in the behavioral program lost more mean body fat, and parents in the behavioral program lost significantly more mean body weight during the first 6 months of enrollment. (n=57, $P<0.05$) [86]. In the future social networking sites may be a venue for health promotion initiatives in the prevention and treatment of obesity related hypertension. Further research is needed to determine the optimal approach to maximize the interventional benefit from such technology.

Medical therapy

If lifestyle modification is unsuccessful BP management should be pursued with pharmacologic therapy. Acceptable drug classes for the pharmacological treatment of hypertension in childhood include angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARB), β blockers, calcium channel blockers and diuretics. The goal of antihypertensive therapy should be the reduction of BP<95th percentile [87•]. The recent Cochrane review of the pharmacological management of hypertension in children evaluated 21 trials of antihypertensive medication. Of these trials, only five compared the antihypertensive agent against placebo. Candesartan (an ARB) led to a significant reduction in SBP (mean difference −6.5 mm Hg, 95 % CI −9.44 to −3.56) and DBP (mean difference −5.5 mm Hg, 95 % CI −9.62 to −1.38) compared with placebo. ACE inhibitors demonstrated a good reduction in SBP and DBP. Both ACE inhibitors and ARBs were found to be relatively well tolerated in children, the most common documented side effect with ARB use was headache, and with ACE inhibitor use, headache and cough were the most common. The efficacy of β blockers is thought to be less in children than in adults and they tend not to be prescribed as first line therapy for hypertension in children. Calcium channel blockers are prescribed frequently for pediatric hypertension, however, the evidence for their BP lowering efficacy is limited [87•].

Yoon et al. examined antihypertensive prescribing practices among privately insured adolescents in the USA. From this investigation it was determined that 69 % of adolescents with primary hypertension were prescribed monotherapy with either an ACE inhibitor or ARB, while up to one-third received combination therapy [88]. The pathophysiology of obesity in adults is thought to lead to activation of the renin angiotensin system, therefore,

ACE inhibitors are theoretically appealing and have become the drug of choice in adults with obesity related hypertension [89].

Conclusion

Obesity-related vascular changes are increasingly recognized as a significant pediatric issue. Arterial stiffness and overt hypertension are increasingly documented in this population and are of significant concern. Both primary and secondary prevention efforts are needed to avert a significant future increase in cardiovascular morbidity and mortality because of the rising worldwide prevalence of this condition concomitant with recent increases in childhood obesity. Existing evidence regarding interventions in children is limited to surrogate markers of adverse health outcomes because of the significant time lag between the onset of vascular disease in childhood and subsequent cardiovascular events in adulthood. Ongoing research to understand the detailed mechanisms of these vascular changes and the best surrogate markers in children is critical to our understanding and management of obesity related hypertension.

Compliance with Ethics Guidelines

Conflict of Interest
Dr. Kathryn R. Armstrong, Dr. Anita T. Cote, Dr. Angela M. Devlin, and Dr. Kevin C. Harris each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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The survey reveals that while obesity prevalence has increased during this time, more recent years show a levelling off, with the exception of an upward trend of more severe forms of obesity. This paper highlights the need for further studies addressing the factors impacting both positive and negative trends.

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