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Review of Physiological and Environmental Risk Factors for Developing Early-Onset Cardiovascular Disease in Obese Children

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Review of Physiological and Environmental Risk Factors for Developing Early-Onset Cardiovascular Disease in Obese Children

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Abstract

Review of Physiological and Environmental Risk Factors for Developing Early-Onset Cardiovascular Disease in Obese Children

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Childhood obesity is one of the greatest health crisis facing developed nations in the modern era. The multifactorial complexity of obesity disease progression, as well as the lifestyle factors that exacerbate it makes it an increasingly difficult disease to prevent. Early onset obesity leads to numerous health conditions, including Cardiovascular Diseases (CVD). Historically, these conditions are diagnosed in later adulthood, although as increasingly younger children are diagnosed as obese, CVD is being diagnosed earlier in the lifespan. A number of biological and environmental factors are causing this rise in childhood obesity, including metabolic disorders and lack of physical activity, as well as socioeconomic variables. Therefore, the primary purpose of this report is to review the literature on the physiological and lifestyle factors that escalate childhood obesity rates and the relationship of obesity to CVD in children under the age of 18. The secondary purpose of this literature review is to examine exercise as a treatment for obesity and CVD in children.

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INTRODUCTION

Childhood obesity is potentially one of the greatest, most widespread, public health crisis facing developed nations in the modern era. Oftentimes obesity is accompanied by the diagnosis of a comorbidity, such as cardiovascular disease (CVD). According to the World Health Organization (WHO), obesity accounts for an estimated 2.6 million deaths worldwide every year; an additional 1.9 million deaths are attributed simply to physical inactivity, as sedentary behavior has long been shown to be a contributing factor in the progression of obesity and CVD (WHO, 2020). Preventing children from developing obesity and reducing sedentary behavior will reduce the number of annual deaths, as the risk for all-cause mortality increases the longer a person remains obese and inactive.

Disturbingly, the prevalence of childhood obesity has steadily increased, especially within the last two decades of the past century and has continued to drastically rise into the present day. At the turn of the millennia, rates of childhood obesity in the United States of America had jumped to 21.5% in African American children, 21.8% in Hispanic children and 12.3% in non-Hispanic white children to the point where one in seven children were overweight or obese (Strauss, 2001 and Swallen, 2004). By 2021, data shows that obesity affects one in five children under the age of 18 in the United States (CDC, 2021). This is a significant increase within a short interval of time and is a trend the US cannot afford to continue over the next few decades.

Consequently, if children remain obese through adulthood, they will accrue a greater financial burden from medical treatments than peers who was never diagnosed with the disease. For instance, adult obese men are estimated to incur $1,152 more in hospital charges per year than normal weight men and obese women incur approximately $3,613 more per year (Hruby, 2015). Even ten-year-old children diagnosed with obesity are estimated to spend $12,660-19,630 more per year than their average weight counterparts in medical costs (Hruby, 2015). In total, the United States expects to accrue around $190 billion per year, roughly 21%, of all medical spending, on obesity-related treatments (Hruby, 2015). Therefore, eradicating obesity before a child reaches adulthood is of the utmost importance to reduce compounding healthcare costs.

Quantifying categories of children's weight is critical when discussing the obesity epidemic. According to the current guidelines, adults are classified as overweight if they have a Body Mass Index (BMI) of 25 to 30 kg/m^2, obese if BMI is $\geq$30 kg/m^2 and morbidly obese if BMI is $\geq$35 kg/m^2 (CDC, 2021). However, in children between the ages of 2 and 19, BMI is age-and sex-specific. A BMI in the $\geq 85^{th}$ to <95 percentile is overweight and greater than the 95^{th} percentile is obese (Hruby, 2015). Children's BMI classifications differ from adults because of the differences in body weight during crucial growth period and the difference in adiposity between young males and females. Numerous research studies have shown a BMI between the range of 19 and 24 kg/m^2 is optimal for reducing the risk of CVD, regardless of age (Brown, 1998).

Behavioral and lifestyle adaptations, such as diet education and regular, consistent exercise, have been shown to be effective at managing the symptoms of childhood obesity and successfully reducing all-cause mortality (Lee, 2001). However, behavioral modifications should be just one of the strategies implemented, as socioeconomic variables further complicate the progression of disease and need to be addressed. Therefore, the purposes of this report are to review the literature on physiological and lifestyle factors causing childhood obesity, the relationship of childhood obesity to CVD development and to examine exercise as a treatment for obesity and CVD in children.

LITERATURE REVIEW

Risk Factors for Childhood Obesity

Age, race and sex are examples of non-modifiable risk factors that predispose a significant portion of the adolescent population to developing obesity. For instance, adolescents are shown to have higher prevalence of disease than younger children: 20.6% of adolescents between the ages of 12 and 19 and 18.4% of children between the ages of 6 and 11 were diagnosed as obese, while 13.9% of children between 2 and 5 were diagnosed as obese (Hales, 2017). This demonstrates either that the older children's longer exposure to an obese-promoting environment causes rates to be higher, or that younger children are still under their guardian's influence and cannot yet make their own dietary or physical activity decisions. It is possible that both situations coexist and once children become more independent from parental influence in adolescence, obesity is more likely to develop.

Racial heritage also determines health outcomes, as children of Hispanic origin have the highest prevalence of disease, followed by non-Hispanic Blacks, non-Hispanic Asians and finally non-Hispanic whites (CDC, 2021). In fact, extreme obesity (greater than the 95^{th} percentile in children) rates have risen from 3.8 to 5.9% and appear to affect Hispanic girls and African American boys disproportionately (Hruby, 2015). This is still unclear physiologically, as obesity is not the only disease to present racial differences. However, there are many socioeconomic variables that may provide insight as to why minorities are more affected by obesity.

Additionally, male children are more likely to be obese than female children, which could partially be due to the timing of puberty. Female children typically cease puberty before male children and may be better adapted to weight changes than their male counterparts. However, higher body fat percentage in prepubescent children may trigger early puberty development, which directly influences weight management in adolescents and may explain the increase of obesity in adolescent children of both sexes (De Leonibus, 2014). Lack of weight control throughout this critical developmental period has been shown to lead to early onset heart disease than their normal-weight counterparts (De Leonibus, 2014). Therefore, prepubescent children should be a major focus for exercise and lifestyle intervention.

Another difference between the sexes could be the difference in brown adipose tissue density, a specialized type of fat correlated to elevated metabolism. Females are known to have higher levels of brown adipose tissue than males, and are able to maintain adequate levels throughout the lifespan (Shah, 2020). This is crucial because an elevated metabolism over time will better maintain energy homeostasis and regulates body weight. Therefore, females are greater protected from becoming overweight for longer periods of time. Unfortunately, this tissue density in determined at birth, so there aren't any training procedures that would increase the amounts found in males. So, other methods of metabolic control must be employed in young males.

Regardless of age, race or sex, the manner in which fat distributes itself across the body influences overall health, depending on whether it encompasses major organs or is more widely distributed. Adipose can congregate around major organs or deposit as subcutaneous fat, commonly in the abdomen, upper arm or upper thigh area (Katta, 2021). The greatest risk for mortality is a high BMI and central obesity, or a high waist to height ratio; while increased thigh girth and higher subcutaneous fat mass is more likely to protect from CVD (Katta, 2021). Likewise, a person with a poor diet and a thick panniculus (dense layer of subcutaneous fat centered in the lower abdominal region greater than three centimeters thick) was twice as likely to be diagnosed with advanced coronary atherosclerosis than a person with poor diet alone (Wilens, 1947). Thus, it is crucial to reduce central obesity and lower the waist-to-height ratio in children before adulthood in order to protect them from developing CVD.

Active lifestyles have been well documented as modifiable factors in attenuating the chronic effects of obesity and sedentary behavior, yet children are increasingly favoring sedentary behaviors in recent years. Exercise time, physical education enrollment, participation in after school sports and active transportation have all declined; meanwhile screen time has drastically increased (Anderson, 2008). Astoundingly, 26.3% of children between the ages of 4 and 11 reported spending less than 7 hours of active play per week and greater than two hours per day of screen time on phones, tablets, computers and TV (Anderson, 2008). Also, there has been a 37% decline in active transportation, such as walking or cycling, for children because cars and public transportation have become more widely utilized (Dollman, 2005). This is a significant decrease in activity and demonstrates the shift in behaviors in response to technological advancements that favor convenience. Physical education enrollment fell from 42% in 1991 to 28% in 2003 and has trended downward since then; participation in organized sports declined as well with 1.5% decrease in one-sport participation and 3% decrease in two-sports participation per year in 9-15 year olds (Dollman, 2005). Overall, there are increasing trends away from active lifestyles and towards more chronic sedentary behaviors, which is worrisome because of the negative effects of inactivity on the development of obesity and its related conditions.

Appetite is also a significant factor in weight management because lack of appetite cessation will lead to overeating beyond metabolic demand, a hyper-caloric imbalance and fat retention. Appetite is modulated by short-term and long-term physiological mechanisms, which influence feeding schedule and adiposity storage, respectively. Afferent signals from the gut either stimulate or inhibit feeding and act as acute controls of food intake (Boswell, 2018). Long-term regulation includes insulin, which regulates blood glucose levels post-prandially and leptin, which decreases appetite and increases thermogenesis (Sadaf Farooqi, 2005 and Boswell, 2018). When any of these appetite-regulating mechanisms are out of balance, a child may gain weight, although leptin may be the key regulator. For example, severely obese Pakistani and Turkish children with homozygous leptin ob gene (ΔG133) mutations presented with nearly non-existent circulating leptin levels (Sadaf Farooqi, 2005). It is thought that this was the main cause of this population's obesity, as leptin therapy was successful in restoring leptin levels and decreasing energy intake by 84% (Sadaf Farooqi, 2005). Furthermore, these leptin-deficient subjects had normal birth weights, but extremely rapid weight gain within the first few months post-partum, which demonstrates the importance of this hormone in weight regulation (Sadaf Farooqi, 2005). But, the converse is detrimental as well. In obese individuals, elevated blood leptin levels are thought to stimulate sympathetic activity, increase myocardial contractility and generate reactive oxygen species, which promotes myocardial inflammation (Alpert, 2018). Exposure to low-quality diet and lowered energy expenditure will only make these conditions worse. Either way, leptin homeostasis is critical for energy balance.

In addition, the FTO gene is identified as being key to energy intake regulation, specifically satiation and calorie intake as it has direct influences on the hypothalamus and its hormonal regulation (Di Cesare, 2019 and Boswell, 2018). Mutations in this gene result in obese phenotypes and disrupted metabolic profiles in young individuals, exacerbated when these individuals are exposed to an obesiogenic environment (Di Cesare, 2019). This kind of environment has many forms, but is commonly a sedentary lifestyle with a high-fat, highly processed diet. These aforementioned genes are only a couple examples of genetic regulations of appetite and weight control, however, it is important to note how genetic predisposition to obesity is exacerbated when a child is exposed to an obesiogenic environment.

Finally, obese mothers are three times more likely to bear infants who have a higher fat mass at birth than mothers of average weight and her risks for all-cause mortality are inheritable and predispose the child to an unhealthy life (Stevens, 2020). Rates of maternal obesity are increasing at a staggering pace, with over half of non-Hispanic Black women of childbearing age characterized as obese (Stevens, 2020). Children born to obese mothers have more adiposity, are at greater risk of developing cardiovascular or metabolic disorders and are more likely to be obese themselves in adolescence and adulthood (Catalano, 2017). Infants exposed to poor diet during development may crave those foods during key developmental years. In an animal model, rat fetuses exposed to fatty, sugary and salty foods in-utero resulted in preference for these kinds of foods early in childhood (Boswell, 2018). This suggests that children who continually consume these foods in early childhood will likely have caloric imbalance, weight gain, and eventually obesity.

Additional Sex Differences

Despite females possessing anthropometric features that predispose them to higher body fat percentages, young males develop obesity at higher rates than females. Between 1983 and 2000, rates of childhood obesity stayed relatively consistent between the sexes, but by 2010, males had significantly higher rates of obesity than previous measures and had significantly higher prevalence than females of the same adolescent age (Kowal, 2016). Plus, the risk of someone suffering from a cardiovascular event, such as a heart attack, in adulthood were significantly lower in females who were diagnosed with elevated BMI in childhood than in males who were diagnosed as obese as a child (Baker, 2007).

Anatomical differences between the sexes, such as body fat distribution at birth and through maturity, as well as hormonal regulatory differences constitute additional non-modifiable risk factors for obesity. Immediately post-natal, females have greater fat-mass and less fat-free mass than infant males; newborn females have higher levels of subcutaneous fat in the trunk region than newborn males, but neither have extraneous visceral fat (Shah, 2020). Then, at the initiation of puberty, females developed more hip and lower extremity fat deposits, while males developed larger waist circumferences (Wisniewski, 2009). This shift in centralized adiposity in male adolescents is one suggestion for the disparities between the sexes because, as discussed previously, central adiposity directly correlates to overall greater risk for obesity and coronary artery disease. Also, young females typically also have lower caloric needs and are less likely to overestimate their food intake than males, which is likely another reason for adolescent males having greater prevalence of obesity (Shah, 2020).

Furthermore, females tend to have higher levels of blood leptin, while males have higher levels of androgen hormones that act to suppress leptin concentration (Shah, 2020). Post-prandial appetite suppression is key to controlling caloric intake and this suggests that females are able to control appetite after satiation better than males. Conversely, it has also been suggested that obese females lack leptin receptors and this is one proposed mechanism of how females develop obesity when their leptin levels are normal (Wisniewski, 2009). In one cohort, 26% of obese females were homozygous for alleles corresponding to a lack of leptin receptors; those with the allele were on average three to four kilograms heavier than those with leptin receptors (Wisniewski, 2009). Overall, leptin homeostasis remains key to controlling appetite and maintaining a healthy weight to reduce the difference in obesity rates in young males and females.

Developing Early Cardiovascular Disease as Direct Result of Childhood Obesity

Complications from CVD are the leading cause of adult death in the United States and are directly correlated to obesity status (Rochini, 2011). One such CVD is coronary artery disease. The odds of someone dying from coronary heart disease was 2.5 times greater in those with a BMI $\geq$ 25 kg/m^2 at 18 years old than someone who had a BMI of 19 kg/m^2 at 18 (Must, 1992). In particular, research estimates that by the year 2035, coronary heart disease will increase to 16% prevalence, and 100,000 of those cases will be attributed to childhood obesity (Rochini, 2011).

Chronic build-up of atherosclerotic plaque in systemic and coronary arteries is a major contribution to the development of coronary artery disease. If the plaque breaks loose, it could block blood flow to critical tissues, such as the brain, heart or lungs, causing ischemic tissue or death. Postmortem studies show that patients with a history of childhood or adolescent obesity have greater atherosclerotic plaque build-up than those never diagnosed with childhood obesity (Rochini, 2011). Studies in living children have also shown that obesity leads to increased thickness of the carotid intima-media, leading to overall endothelial dysfunction (Freedman, 2008). Children with elevated BMI's typically have higher levels of blood lipids, lipoproteins and higher blood pressure, all of which lead to stiffer carotid intima-media in older adulthood (Freedman, 2008). Stiffer vessels are less responsive to local endothelial vasodilatory stimuli, which would make it difficult to dilate systemic arteries in response to acute exercise.

Losing the ability to vasodilate in response to exercise stimuli will cause an increase in peripheral resistance and cause the heart to work harder to circulate blood. In one cohort, obese children between the ages of 11 and 18 were diagnosed with brachial artery dysfunction in a graded manner, in which higher levels of body fat percentage were correlated to greater dysfunction (Maskova, 2014). This is especially problematic because vascular endothelial dysfunction in childhood is a marker for future cardiovascular complications, such as hypertension (Cohen, 2004). So, it is reasonable that those children with higher fat percentages are at greater risk for developing hypertension. Uncontrolled hypertension can be fatal as it may lead to congestive heart failure when the myocardium is no longer strong enough to overcome the increased resistance. As children are diagnosed with obesity earlier in the lifespan than previous generations, controlling hypertension becomes increasingly important to prevent early disease or death.

Even if obese children are not diagnosed with CVD, coronary artery disease or hypertension before adulthood, children who remain obese through adulthood develop chronic diseases much earlier in the lifespan (WHO, 2020). Obese children are at 3.3 times more risk of developing systemic hypertension than their normal-weight counterparts and are also more at risk of developing ischemic heart disease, congestive heart failure, left ventricular remodeling and stroke (Cohen, 2004). But in children whose disease progression is still relatively new, there is hope of reversing these disorders.

Cardiovascular Remodeling

In addition, obese children diagnosed with hypertension are more likely to have pathological increases in left ventricular mass and diastolic dysfunction in adulthood than obese children who are not hypertensive (Cohen, 2004). Cardiovascular remodeling affects the overall function of the heart and its effectiveness at delivering nutrient-rich blood to working tissues. Needless to say, both normo- and hypertensive obese children are at greater risk for pathological changes than children who have never been obese (Cohen, 2004). In athletic populations, cardiovascular hypertrophy actually improves performance, but in chronic heart disease patients, it exacerbates cardiovascular dysfunction.

Uncontrolled hypertension increases peripheral resistance and increases blood pressure to dangerous levels at rest, so patients with hypertension must be carefully monitored during exercise. Approximately 50-60% of the obese population is hypertensive and have significantly greater left ventricular mass regardless of the severity of obesity; and the longer the obese patient is diagnosed with hypertension, the greater the left ventricular mass (Alpert, 2018). This is because the longer duration of increased peripheral resistance, the longer the heart can build muscle mass to compensate for the increased peripheral resistance.

Moreover, normotensive obese patients are expected to develop eccentric left hypertrophy, while those with hypertension are likely to develop concentric left ventricular hypertrophy (Lauer, 1991). Overall, developing eccentric hypertrophy would be preferred to concentric in this case, as the left ventricular chamber remains the same size. The patient would be able to maintain adequate left ventricular diastolic volume, end systolic volume and ejection fraction. All of these are crucial to adequate blood distribution, especially in heart failure patients. Concentric hypertrophy would reduce the size of the chamber and lead to lowered diastolic volume, decreased ejection fraction and cause the heart to work harder to deliver adequate blood supply. Decreasing cardiac output through this mechanism would significantly limit the volume of exercise a patient could sustain safely. Therefore, it is imperative to control hypertension in obese children because they have the potential to remain hypertensive through adulthood and develop these irreversible cardiovascular changes.

Quality of Life and Life Expectancy for Obese Children

Physiologically, disruptions in metabolism, energy expenditure and imbalanced appetite put children at greater risk for obesity and metabolic disorders. Metabolism maintains caloric balance and is crucial for successful weight management throughout the lifetime. Imbalances in caloric intake cause metabolic disorders and can lead to weight gain in children and adults (Weiss, 2004). Metabolic disorders encompass multiple signs and symptoms, including increased adiposity, high waist circumference, insulin resistance and hypertension (Weiss, 2004). When controlling for race and ethnicity, the prevalence of metabolic syndrome in obese and overweight children increased proportionally to obesity severity, reaching 49.7% prevalence in severely obese children (Weiss, 2004). In fact, each half-unit increase in BMI significantly increases the odds for insulin resistance and the promotion of pro-inflammatory markers (Weiss, 2004).

Metabolic syndrome in youth causes hypertension and insulinemia, which could progress to hypertension or type II diabetes in adolescence even though type II diabetes is typically diagnosed in adult populations (Maskova, 2014). In fact, children classified with body fat greater than 39% reported significantly higher levels of hyperglycemia, hypercholesterolemia, hyperinsulinemia and insulin resistance than their counterparts who had just 7% less body fat (Maskova, 2014). Insulin resistance in childhood, coupled with the natural decline in insulin sensitivity brought about at puberty creates an opportunity for type 2 diabetes to develop if the child is exposed to an obesiogenic environment (Hannon, 2005). A longitudinal study found that those with higher BMI levels in childhood had significantly higher insulin and triglyceride levels, an overall 8.4 kg/m^2 BMI increase and 1% of the participants were then diagnosed with type II diabetes in a 17-year follow-up (Freedman, 2001). However, exercise and lean body mass may be the key to reversing the effects of metabolic disorder. Greater muscle strength and higher aerobic capacity are inversely related to metabolic syndrome incident and risk of disease (Roberts, 2013). Some examples of exercise interventions will be discussed in subsequent sections of this review.

Other complications of obesity include developing obstructive sleep apnea, which would either affect the delivery of blood to myocardium, or negatively affect the lung's ability to adequately oxygenate blood. Men diagnosed as obese in childhood have 31% higher risk of developing obstructive sleep apnea, while women diagnosed as obese in childhood have a 51% higher risk of being diagnosed with obstructive sleep apnea (Borgeraas, 2018). Patients report difficulty sleeping on their backs as it becomes difficult to breath, which is due to the large abdomen pushing on the diaphragm and limiting thoracic cavity expansion. Sleep apnea is problematic, not only because it affects the quality of sleep, but also because chronically deoxygenated blood will cause long-term fatigue (Borgeraas, 2018). Patients experiencing chronic fatigue will be less likely to want to expend precious energy exercising, thus sleep apnea becomes a consideration to exercise therapists. So, decreasing central obesity in children will alleviate the pressure of the abdomen on the diaphragm and reduce the likelihood of developing sleep apnea.

Elevated childhood BMI increases the likelihood of either a fatal or nonfatal CVD event, such as a myocardial infarction or stroke, in adulthood. In fact, a 13-year-old boy of the same age and height, but 11.2 kg heavier has a 33% higher risk of experiencing a cardiovascular event in comparison to a boy who is normal weight (Baker, 2007). And, childhood BMI was directly correlated to fatal adult CVD events in individuals diagnosed as obese at ages seven to thirteen (Baker, 2007). Plus, individuals categorized as obese in childhood were at an increased risk of stroke in comparison to their normal-weight counterparts, with a greater risk for those strokes to be fatal (Lawlor, 2005). Therefore, obese children are at a significantly greater risk for experiencing a CVD related event in adulthood than their normal weight counterparts and interventions must be made early in order to prevent such an event.

Geography

Geographical and sociopolitical variables must be taken into account when discussing the childhood obesity epidemic. The geographical region of the United States in which a child resides, and the different communities within that region, play a role in health management. An obesiogenic environment index show the highest rates of childhood obesity occur in the Southern region of the United States, followed by the Western, Midwestern and Northeastern regions, respectively; rural counties had significantly higher rates of obesity than metropolitan counties (Kaczynski, 2020). This is an intriguing finding considering there are fewer spaces for children to play in large cities than in rural communities, where green spaces are likely more frequent and larger in size. For instance, in the city of Manhattan in New York, there are over 1.1 million people who live in areas that lack a park within a ten-minute walking radius (Hu, 2020). Furthermore, the park size within poorer boroughs is much smaller, averaging 6.4 acres, while richer boroughs have parks averaging 14 acres (Hu, 2020). Therefore, a lot of lower income children must rely on schools to provide physical activity, either through recess or physical education.

Individual communities prioritize different diet, exercise and other lifestyle choices, which can predispose certain communities to chronic disease if poor diet and sedentary behavior are lauded. For example, children raised in the Southern United States, or in rural communities, are at the greatest risk of developing chronic obesity (Kaczynski, 2020). There are several factors at play, but certainly fatty diet and lower access to health facilities for regular medical examinations play a role (Kaczynski, 2020). Further investigation determined that rural Black children had the highest risk of obesity, consumed more fatty snacks and averaged more screen time than their white metropolitan counterparts (Kenney, 2014). Racial differences are another component to the discussion of obesity progression in children; but this demonstrates that, although urban areas may have greater access to high fat foods, rural dwellers may buy highly preserved foods because they may make infrequent trips with long commutes to the nearest store.

In addition, those in lower-income communities may not have access to fresh fruits and vegetables, or have limited access to them, while those in richer areas are likely able to access fresh foods easily. In urban areas, food deserts are common, and poorer communities likely do not have access to supermarkets or farmers' markets that sell fresh fruits and vegetables. Instead, lower income communities have to rely on corner markets, convenience stores or large superstores to purchase food (Stern, 2016). Oftentimes, these are quite a distance from the home, which makes trips to these stores infrequent. Lack of access to car or public transportation may make this even more of a challenge. Thus, the purchase of foods that have a long shelf-life (e.g. highly processed and preserved foods) is the more logical, if less healthy, choice (Stern, 2016). The highest number of processed foods, such as savory snacks, desserts and soft drinks, were found in mass merchandise stores, warehouse-bulk stores and conveniences stores, while the lowest numbers of these types of foods were in grocery stores (Stern, 2016). It is important to note that there may be familial ties or monetary restraints keeping a family in a less affluent area, so the option of moving geographical locations is not feasible. Therefore, support for local grocery stores must be prioritized in food scarce areas in order to maximize the health benefits of availability of fresh produce. Affordable and accessible public transportation must be a priority in low-income and rural communities, as well.

Race and Ethnicity

Obesity, CVD and hypertension disproportionally affect non-Hispanic Black individuals more than whites (Anderson, 1989). Young African American girls reached puberty, began menses earlier than their white counterparts and had an average 2.3 kg/m^2 higher BMI than their white counterparts (Kimm, 2001). By the age of nine, a cohort of Non-Hispanic Black and Non-Hispanic white girls all had skinfold measurements that classified them as overweight and at greater risk for coronary heart disease, however blood lipoprotein was three times higher in Black girls than white girls (Clinton Smith, 2004). Then, by the age of twelve the skinfold measurement of the Black girls had surpassed the white girls (Clinton Smith, 2004).

It has also been shown that Black individuals have approximately 295 kJ/d lower resting energy expenditure than age-controlled white individuals, which suggests that there is the potential for Black girls to overestimate their caloric needs (Gannon, 2000). In addition, by the age of 17, as many as 56% of total Black girls in one study reported no extraneous physical activity outside of school-based physical education in comparison to 31% of the white girls studied (McNutt, 1997). Even after accounting for socioeconomic factors, Black girls were still more likely to choose these poor health practices, both at initial review and in a five-year follow up, such as increased television viewing and eating when not hungry (McNutt, 1997). Further studies are needed to determine why obesity and CVD affect Black individuals more than white and if there are racial differences in obesity status in Hispanic and Asian communities, comparatively.

Socioeconomic Variables

Socioeconomic status has an incredible impact on quality of life and resource availability, including affordable food and transportation, as well as access to youth activity centers, outdoor recreational areas, and parental ability to transport children to these recreational facilities. Parents would need to have flexible jobs, steady income, childcare and health insurance in order to meet the demands required to provide quality food and to ensure adequate time and resources available for children to have healthy diet and exercise. This is simply not a reality for many families in the United States.

Food prices are continuously increasing, thus widening the divide between lower class and middle-to-upper class. Lower-income families are thereby forced to pick inexpensive, less-nutritious foods to stay within budget, even though those low-quality foods have been shown to lead to weight gain in large quantities (Kern, 2017). It has been well documented that poorer areas lack resources to low-cost fruits and vegetables, but are able to access cheap high-fat highly-processed food and there is a direct, inverse relationship between higher-priced, healthy foods and a lower-quality diet (Kern, 2017 and Stern, 2016). If wages remain stagnant in lower income groups and food prices continue to increase, families will be unable to afford fresh produce altogether and the obesity crisis will only worsen.

It has been shown that childhood obesity was at 18.9% in the lowest income group, compared to 10.9% in the highest income group for children between the ages of 2 and 19 (CDC, 2021). This is a significant difference and can be directly linked to the quality of food available to those individuals. Low-income, predominantly Black or predominantly Hispanic minority communities have 29% fewer healthy products in their local stores than high-income white neighborhoods (Zenk, 1971). Lack of access to nutrient rich foods will only further exacerbate obesity levels in lower income children, and especially children in minority communities. In fact, students who attended highly economically disadvantaged schools in Texas were 1.7 to 2.4 times more likely to be obese than those that attended less economically disadvantaged schools across all ethnicities (Springer, 2015).

Unfortunately, those underfunded schools that cannot provide nutritious student meals, likely do not have resources for physical activity education, as well. The Georgia public school system, for instance, reports that only 58% of schools have a playground on school premises and lower funded schools were less likely to report access to playgrounds or blacktops than their wealthier counterparts (Van Dyke, 2018). Increasing funding to these underprivileged schools towards physical education, as well as a more inclusive school-lunch program, may help decrease this gap in resources. It is reasonable to conclude that by giving children from lower socioeconomic classes access to food assistance programs and comparable playground equipment as higher-income schools, levels of obesity will likely decline in these communities without additional intervention.

COVID-19 Pandemic

The global Sars-CoV-2 pandemic, as well as the lockdowns and curfews it forced upon the global population, has made it increasingly difficult to gain access to proper nutrition and to meet physical activity recommendations. Low-income areas that have already reported food insecurity in the past have been impacted more than wealthier areas (Zemrani, 2021). For instance, in April 2020, 93.5% of respondents to a survey of four geographical regions in the United States reported themselves as being food insecure and 41.4% of the total number of respondents reported a decrease in fruit and vegetable consumption in response to the pandemic (Zemrani, 2021). The rise in food insecurity and poor nutrition choices has led to an increase in weight gain over the course of the pandemic as citizens were encouraged not to leave their homes except for essentials (Zemrani, 2021). Conversely, under-nutrition or malnutrition is expected to affect 6.7 million children worldwide due to declines in familial incomes, unavailability of affordable food, or loss of social income programs that help feed underprivileged families (Headey, 2020). Therefore, children are more at risk for death or serious disease during the COVID pandemic, not only due to risk of infection of the virus itself, but starvation or long-term consequences of developing obesity-related illnesses.

As schools transitioned to an online platform, curfews were enacted and other means of social distancing began taking effect. Children began spending more time in front of screens and less time exercising or being active. In fact, 87% of children studied in a cohort had elevated screen time than at the same time the previous year (Sultana, 2021). Overall, they averaged a screen time of approximately 6.4 hours per day, which is significantly higher than the recommended screen time limit of two hours or fewer per day for children (Sultana, 2021). This increase in sedentary behavior is worrisome in children and adolescents, not only because this is a critical time period for developing lifelong health habits, but also because they are not meeting the recommended guidelines for physical activity. Instead, kids are increasing their time spent on devices, either for online schooling or social media and gaming.

Active transportation to school, physical education classes, as well as school-sanctioned and club sports were postponed due to the lockdowns. These declines in activities of daily living are likely to show long-term effects on children's overall health, sedentary levels and BMI. In a group of healthy, adolescent males, reducing the daily step count from 10,000 steps to 1,400 steps per day for 3 to 5 days per week was enough to decrease insulin sensitivity and glycemic control on endothelial function (Smirmaul, 2020). In addition, two to three weeks of sedentary behavior was enough to reduce maximal oxygen uptake ($VO_{2\ max}$) by 7% and increase visceral adiposity levels by 7% (Smirmaul, 2020). Adding these declines in physiological function to the detriments already observed in obese children could escalate disease progression further and worsen the effects of the pandemic more than normal-weight children forced into this sedentary situation.

Therefore, one suggestion is exercising at home during lockdowns, using either purchased gym equipment or household items that could double as free weights, such as soup cans or water bottles to attenuate sedentary behaviors. Exercising at home with the immediate familial unit is an excellent way to engage the whole family while still promoting recommended social distancing measures. Children should be encouraged to continue active play in a distanced manor and with immediate family members in addition to online school physical education. The goal is to partake in at least thirty minutes of moderate physical activity every day or twenty minutes of vigorous activity every other day; this can be accomplished through walking in neighborhoods, climbing stairs, sitting-to-standing activities, squats, sit-ups, pushups, as well as yoga and Pilates via internet classes (Chen, 2020). These are all excellent activities that will help improve or maintain a child's physical and mental status, regardless of if they are obese.

However, certain considerations must be made for patients who have just recovered from coronavirus. Even though coronavirus is a respiratory disorder, serious side effects have developed immediately after recovery including physical disabilities, such as muscular weakness, disjointed movement and central or peripheral nervous system dysfunction (Scudiero, 2021). Additionally, patients may have lost an incredible amount of weight and muscle mass, so their fitness may not be at the same level it was pre-infection (Scudiero, 2021). And, those children with underlying heart conditions will need additional safety measures, as well as monitoring by a cardiac rehabilitation specialist (Scudiero, 2021). More worrisome still is an emergence of a complication of COVID-19 identified solely in children. A small population of children who have recovered from SARS-CoV-2 were diagnosed with Multisystem Inflammatory Syndrome, leading to significantly increased intracranial pressure and neurological changes in the central and peripheral nervous system further causing encephalopathy, headaches, muscle weakness and reduced reflexes (Baccarella, 2021 and Abdel-Mannan, 2020). Obviously, more research must be conducted on these complications, since the virus is still relatively new and there continues to be emerging side effects. But, all of these acute consequences need to be taken into account when developing an exercise program for a child who has just recovered from the COVID-19 virus.

Exercise as Treatment for Obesity

Exercise intervention is well documented as the gold standard for weight control and reducing all-cause mortality in obese populations. Despite this knowledge, obese children remain inactive. It is no surprise that it is difficult for overweight children to exercise as there are various physical and psychological barriers to exercise in this population. Developing interventions becomes difficult if children are unwilling to participate, so these exercise specialists must be aware of these barriers to make the activities as engaging to all children as possible.

Already, few children, regardless of fitness level, do not meet the proposed weekly physical activity recommendations. In fact, physical activity has been shown to decline as early as seven years old and continues to decrease through adolescence (Farooq, 2018). This could be due, in part, to a number of reasons: stress, homework, afterschool activities, part-time jobs, family income worries, disrupted sleep, geographical residency, race, etc. Nonetheless, the 2018 Physical Activity Guidelines recommends that preschool age children (ages 3 to 5 years old) should engage in active play, such as riding a bicycle or playing with peers, and strengthening activities, such as skipping and jumping, for about three hours per day (Piercy, 2018). Adolescents (ages 6 to 17 years old) should engage in 60 minutes or more of moderate-to-vigorous physical activity daily that meets requirements for aerobic, muscle-strengthening and bone-strengthening activities (Piercy, 2018). These are reasonable recommendations, which is why it is so problematic that children are not even able to meet them. Perhaps policy changes to reduce homework load or increase physical activity within the school day should be put into place in order to allocate enough free time to meet the physical activity guideline suggestions.

One suggestion is to approach exercise treatment in obese children differently than adults. For example, children will not be able to participate in prolonged exercise without taking frequent rest periods as they do not possess the stamina adults have and free, active play is a better exercise strategy for children than a rigorous, structured program (Sothern, 2001). Overall, Janssen et al. determined that any effective exercise intervention for obese children aged 5-17 should include three basic elements: an average of 60 minutes or longer moderate physical activity per day; vigorous activities should be incorporated into this time, including bone and muscle strengthening activities three times per week; and, aerobic activities should make up the majority of the physical activity (Janssen, 2010). Unlike adults who typically get their exercise in an indoor gym environment, young children should be encouraged to play outdoors as much as possible; not only for the benefit of exercise, but also for psychosocial and sensory development (Sothern, 2001). Making new friends and engaging in the environment is key for children's overall health, so it is imperative to provide children with an inclusive environment to enjoy activities.

One of the barriers to exercise for obese children is feeling isolated from peers who are more physically active. They oftentimes feel embarrassed that they cannot move in the same way as other children, or they are often left out of activities and are ridiculed for their appearance (Javernick, 1988). So, they tend to avoid these situations by staying indoors during recess or participate in other sedentary behaviors away from their antagonists (Javernick, 1988). This behavior is detrimental, not just to physical fitness, but also social development, as well.

Not to mention, another barrier to exercise is overweight children often experience discomfort or pain during movement, which could limit their exercise tolerance or cause injury (Sothern, 2001). Either of these situations would greatly increase noncompliance of exercise recommendations and prevent obese children from gaining the benefits of exercise, reduced weight and decreased risk for CVD (Sothern, 2001). One suggestion to combat these barriers is to ensure these children leave the intervention with a positive attitude towards physical activity (e.g. making it feel less like a chore) and to design a program that implements more intermittent activity throughout the day in an effort to minimize discomfort by limiting the time spent upright (Dobbins, 2013). It is important for educators to be aware of these barriers to movement so they can better help obese children meet the Physical Activity Guidelines in a safe manor.

When beginning an exercise program, each child should go through an exercise stress test because it is the best way to assess multisystem health and overall fitness. Unless diagnosed with abnormal heart rate, heart rhythm, or any other cardiovascular complication that contraindicates exercise, children are safe to be screened with an exercise stress test, much like adults (Stephens, 2004). These contraindications include severe heart disease, severe hypertension, acute musculoskeletal injury, right or left ventricular dysfunction, heart valve malfunction, pulmonary hypertension, or severe ECG arrhythmias (Stephens, 2004). So, children who are at greater risks for these conditions may need additional medical attention before beginning an exercise program. When attached to a heart rate monitor, rehabilitation specialists can effectively measure heart rate and rhythm to ensure safety and performance standards. There are many different stress tests that are adapted for the treadmill and the cycle ergometer, however their general purpose is to determine the upper limit of cardiovascular fitness, how well participants respond to increasing levels of exercise intensity and establish a baseline for further exercise programs (Stephens, 2004). And, finally, a stress test should always be done before and after an exercise intervention to ensure safety in the program and track progress through the intervention.

The exercise recommendations from Louisiana State University Health Sciences Center state that overweight and obese children follow a one-year exercise program in an outpatient clinical setting. According to the model, participants and their families must attend weekly classes aimed at medical, nutritional, physical, behavioral and exercise instruction, overseen by medical professionals (Sothern, 2001). They also provide a graded exercise program based off of obesity status classified by BMI. For overweight children (<150% Ideal Body Weight or >85-95th percentile BMI), aerobic, weight-bearing activities, such as brisk walking, jumping rope, and swimming, dancing or playing tag is recommended for two hours almost every day (Sothern, 2001). Obese children (150-200% Ideal Body Weight; >95-97th percentile BMI) should focus on non-weight bearing, aerobic activities, such as swimming, cycling, interval walking or arm ergometer every day for as long as it is tolerated, stopping for breaks when needed (Sothern, 2001). Finally, severely obese children (>200% Ideal Body Weight; >97th percentile BMI) should be monitored by medical professionals, and should engage in non-weight bearing aerobic exercise, such as reclined bike, arm ergometer or chair aerobics, only for as long as tolerated (Sothern, 2001). By providing recommendations for each weight class based on what is physically feasible, it will give the children of each weight class confidence to perform activities that can be physically tolerated and set new, achievable goals.

Both endurance and strength training have been shown to be effective means of reducing weight and all-cause mortality in children with obesity. In teenage children who did not participate in athletics, there was little difference in exercise economy or VO_2 peak between chronic single-mode endurance training and strength training (Geabler, 2018). However, concurrent training (a combination of endurance and strength training in a single bout of exercise) has been shown to have greater improvements in time trial speed and VO_2 peak than endurance training alone and greater improvements in muscle power output than strength training alone (Geabler, 2018). Additionally, cross training has been shown to improve markers of cardiorespiratory fitness in youth, which are directly correlated to lower body fat percentages and lower waist circumferences (Mintjens, 2018).

Therefore, a suggested physical education approach includes a series of stations where some focus on strength building exercises, such as climbing stairs, jumping rope, or even light weights; and, other stations which focus more on cardiopulmonary endurance, such as sprinting or stationary bicycles, and have the student rotate through the stations during the allotted time. Different days could focus on different muscle groups, or introduce high-intensity interval training into the program to improve VO_2 peak to a greater extent (Geabler, 2018). Regardless of the modality, this is an excellent opportunity to encourage children to decide the type of exercise best suited to them. If children enjoy the physical activity, they will be more likely to participate in it outside of the school setting, which should be the main goal of an intervention strategy.

As obese children continue to increase activity levels, they will likely experience reductions in insulin sensitivity, decrease the effects of metabolic syndrome, reduce weight and attain a healthier BMI. Interval training was shown to restore endothelial function, insulin signaling and blood glucose regulation better than strictly aerobic training (Roberts, 2013). In a 14-day intervention where diet was controlled with high-fiber, plant-based meals, symptoms of metabolic syndrome were attenuated in all of the participating children when this diet was combined with two hours of exercise games per day (Roberts, 2013). This suggests that, long-term exercise intervention could potentiate this effect and could lead to additional weight loss than diet or exercise alone in this population. In fact, insulin sensitivity is a main improvement from exercise and obese individuals are likely to see improvements in insulin signaling proteins, such as GLUT-4 membrane protein sensitivity (Roberts, 2013). Better insulin sensitivity will lead to better glucose uptake in cells, better fuel utilization and reduced fuel storage in fatty tissue. Effectively, these diet and exercise interventions will reduce symptoms of metabolic disorders, lower adiposity levels and improve obesity levels in children.

Also, adolescents diagnosed with American Heart Association class C or D heart failure who underwent a bout of outpatient cardiac rehab increased their six-minute walk distance by an average of 111 meters (Wittekind, 2018). Those that completed a 12-week session of cardiac rehab had significant improvements in BMI, body fat percentage, VO_2max, low- and high-density lipoprotein cholesterol, triglycerides and fasting levels of glucose (Lavie, 2009). A six-month long cardiac rehabilitation program restored endothelial function in obese adolescents, by decreasing intima-media thickness by 6.3% and increasing Flow-Mediated Dilation (FMD) by 127% (Meyer, 2006). Patients who lost the most amount of weight in cardiac rehabilitation trended towards a lower risk of mortality in a three year follow up than those that did not lose as much weight (Lavie, 2009). This demonstrates that exercise in an outpatient cardiac rehabilitation setting significantly improves risk factors that lead to fatal or nonfatal cardiovascular events in overweight and obese adolescents.

One consideration for children who have increased fat-to-lean body mass ratio is that obese children must carry this additional weight through the same activities and range of motion as normal-weight children. This will put extra strain on muscles and joints to perform the same motion and it is important to make sure these children do not sustain a musculoskeletal injury. Therefore, tracking bone density over the course of an exercise program is an important safety measure, especially for overweight children who have never exercised before. Strength training has shown significant increases bone density and effectively reduces the chance of musculoskeletal injuries (Larson, 2016). In fact, ten-month cross-training intervention for obese youth implemented in primary schools showed an 8 mg/cm^2 and 7 mg/cm^2 increase in bone mineral density for small-group ball game and circuit training, respectively (Larson, 2016). Therefore, exercising interventions that combine strength and endurance activities will be the most beneficial for obese children because the risk for injury decreases.

Introducing intermittent physical activity throughout the school day will improve attention and memory in addition to reducing weight. Physical activity brain breaks given in the middle of a lesson are intended to help children remove some energy from their system and refocus on the learning activity (Ahamed, 2007). These short (usually a few minutes long) bouts of physical activity engage children and allow them to take a break from their learning activities and have been shown to have positive effects on acute memory and attention (Ahamed, 2007). This is an excellent strategy, since additional movement throughout the day not only correlates to higher daily energy expenditure, but also improves markers of academic success. Both of which are beneficial to physical and mental development of students. In fact, these intermittent activity breaks in primary schools increase reading and mathematical fluency, improve children's attitude towards school and decrease feelings of tiredness and increase mental stamina for a lesson (Wold, 2019; Duke, 2018; Lotta, 2015). Improving mental performance in school will increase motivation during lessons and also increase energy needed to continue physical activity throughout the day.

Additionally, there are numerous, effective after-school programs implemented at the local level to promote movement and exercise in youth. Two notable long-term programs are the Healthy Hearts Program in Colorado and the Fun and Fit Program in Massachusetts. The first focuses heavily on prevention and education, while the latter focuses more on exercise intervention. The Healthy Hearts Program is tailored for elementary, middle school and high school levels and includes education on basic cardiac anatomy, cholesterol, blood pressure, BMI, healthy diet and nutritional labels, portion control, risks of smoking and the benefits of exercise, followed by cholesterol and BMI evaluations of students (Puccetti, 2016). In a follow-up, 50% of middle school students who attended the educational training planned to increase their exercise by 10 minutes a day, 44% of high school students planned to increase their exercise duration and 96% of elementary school children showed improved health behavior six months after the program (Puccetti, 2016). This demonstrates that effective education increases the desire to be active and increases the likelihood that children will begin or maintain an exercise program.

The Fun and Fit Program was an after-school program for elementary children that incorporated cardiovascular activities, strength training, meditation, group support and nutritional counseling and was led by experts in exercise and nutrition (Gruenfeld, 2013). Each session combined 45 minutes of various cardiovascular machines, such as elliptical or treadmills, and 30 minutes of yoga or meditation. At the beginning of the program, 95% of the participants were obese, and after an 8-week intervention program, male's VO_2 max increased from 39.5 ml/kg/min to 47.5 ml/kg/min, female's VO_2 max increased from 31.2 ml/kg/min to 33.8 ml/kg/min and BMI trended downward (Gruenfeld, 2013). This suggests that prolonged exercise intervention is effective in improving markers of health in obese children and will continue to improve with long-term training. A successful intervention strategy should always combine lifestyle, nutrition and weight management education with physical activity because children as young as elementary schools have demonstrated the ability to integrate the provided information into increased activity.

Finally, parents, or guardians, should perhaps be the main targets in childhood obesity intervention because they are instrumental in implementing the intervention strategies in the child's daily life. Coaching obese children and their parents together on nutrition and exercise, placing children on a balanced, hypo-caloric diet and biweekly training sessions which mimicked activity levels of age-matched average school children for three months significantly decreased body weight, body-fat percentage and BMI (Nemet, 2005). In a yearly follow-up, these trends continued, while body weight, body-fat percentage and BMI increased in the controls who were not coached throughout the intervention (Nemet, 2005). This actively demonstrates the need for parents to be involved in the child's exercise and nutrition program, as they are likely the ones in control of food preparation and scheduling daily exercise bouts.

SUGGESTIONS FOR FUTURE RESEARCH ON CHILDHOOD OBESITY

Future studies regarding the effects of childhood obesity on early diagnosis of CVD should include more longitudinal studies that examine the chronic progression of the disease. This would create a detailed, chronological description of each parameter of the disease, as well as provide insight on where interventions could be optimally utilized. This kind of study should optimally begin in infancy and continue until the child reaches adulthood. Parameters to measure should include metabolic profiles, height and weight characteristics in comparison to age-matched controls, activity levels, sport involvement, VO_2max and cardiac stress test results, cardiac anatomy and any cardiovascular changes that occur throughout the study. Cardiovascular remodeling is another area that needs more focus, especially since these changes have been shown to begin in adolescence.

Additionally, studies that examine the long-term consequences of the COVID-19 virus are needed to determine how side effects of the disease impact physiological function, especially the Multisystem Inflammatory Syndrome in children. Also, it will be interesting to determine the physiological effects of online and hybrid-learning situations brought on by the pandemic. The physical education quality of the online platform should be compared to preexisting data from before the pandemic to see if there have been declines in the quality of education provided and what the effects of moving online have on weight status of children.

CONCLUSION

In conclusion, the overwhelming prevalence of childhood obesity makes it ones of the greatest public health challenges in modern times. Obesiogenic environments provide more opportunity for obese children to develop CVD much earlier in the lifespan than those who were not diagnosed with obesity in childhood. Physical activity interventions, as well as social assistance programs must be implemented in order to reduce the effects of and obesity-promoting environment.

Non-modifiable risk factors, such as age, race and sex predispose some individuals to obesity in childhood. Older adolescents, racial minorities and males present with obesity at greater rates than their respective counterparts. Young females have greater leptin levels and sensitivity, greater brown adipose tissue density and less visceral fat than young males. Racial minorities, specifically non-Hispanic Blacks, seem to have hereditary predisposition to obesity. Regardless of the risk factor, central adiposity, poor diet and lack of physical activity augments obesity. Genetic factors and maternal health greatly impact birth weight and can start a child off with a physical disadvantage.

Childhood obesity significantly increases the chance of developing CVD earlier in the lifespan and significantly increases the chances of dying from a fatal CVD event. Endothelial dysfunction can greatly increase the total peripheral resistance in the systemic arteries and lead to hypertension; if left uncontrolled, hypertension can lead to cardiovascular remodeling and chronic heart failure. Childhood obesity also makes the early diagnosis of metabolic disorders commonplace and can even lead to type II diabetes.

Therefore, future strategies to combat the childhood obesity epidemic should include exercising strategies that combine diet, metabolic, cardiovascular anatomy education to parents and children with exercise intervention. A combination of strength and aerobic exercises will maximize reductions in metabolic and endothelial dysfunction and improve markers of physical fitness, such as higher VO_2max and lower hypertension. Future interventions should look towards the Healthy Hearts Program and the Fun and Fit program for fitness integration examples. Additionally, implementing brain breaks in the middle of academic lessons will not only improve cognitive performance, but also increase caloric expenditure and promote extra movement outside school. However, the COVID-19 pandemic brings with it another complication as lockdowns prevent outdoor activity and limit the availability of fresh food. Not to mention, side effects from the disease may make returning to an exercise regimen more dangerous as complications include heart and muscular dysfunctions, as well as Multisystem Inflammatory Disorder in some children who have recovered from the disease.

Also, modifiable socioeconomic, geographical and racial disparities must be addressed in future interventions because these variables are directly tied to children's fitness. Making affordable foods available in lower-income neighborhoods and expanding food assistant programs will lesson the divide between these neighborhoods and more affluent ones. In addition, providing safe and comparable exercising areas for children will also encourage lower-income children to meet the recommended physical activity guidelines. Rural communities need better closer access to grocery stores and exercise needs to be prioritized out in the country, while urban communities need better access to high-quality, low-cost foods and community parks or recreation areas. Finally, continued research is needed to determine the mechanistic explanation for racial disparities in developing childhood obesity and CVD.

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Vita

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