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REVIEW ARTICLE

# Acute Myocardial Infarction in Young Patients and its Correlation with Obesity Status at Pre-adolescent Stage: A Narrative Review

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**Abstract:**

***Background:***

Cardiovascular diseases (CVD), especially acute myocardial infarction (AMI), remain a worldwide major cause of premature morbidity and mortality, with considerable health care costs. Metabolic, behavioural, environmental, and social risk factors are significant drivers of AMI, with obesity being a key determinant among them. Childhood obesity constitutes a major health threat that is considered a global epidemic of the 21st century.

***Objective:***

To assess whether excess weight from the first years of life acts as a predisposing factor in increasing the risk of AMI in young adults.

***Methods:***

This is a narrative review of the evidence concerning the epidemiology of early AMI and obesity, using PubMed and Google Scholar.

***Results:***

There is substantial evidence showing that excess weight during childhood multiplies the risk of AMI at an early age.

***Conclusion:***

Premature AMI seems to have significant drivers related to lifestyle factors, such as childhood obesity. In the era of a childhood obesity epidemic, the aforementioned relationship underlines the need for early prevention and management.

**Keywords:** Myocardial infarction, Cardiovascular disease, Ischemic heart disease, Obesity, Childhood, Adolescence.

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## 1. INTRODUCTION

Cardiovascular diseases (CVDs), and particularly coronary heart disease (CHD), are the leading cause of morbidity and mortality globally [1, 2]. Despite considerable improvement in diagnosis and therapeutics, up-to-date epidemiological data from the Global Burden of Disease (GBD) [3] reports that 126 million individuals (*i.e.*, approximately 1.72% of the world's population) are affected by CHD [3]. Acute Myocardial Infarction (AMI) is responsible for >15% of worldwide mortality each year [4]. Although the incidence of AMI tends to decrease in industrialized nations, partly because of enhanced health systems and effective public health strategies, the AMI rates are surging in the developing countries (*e.g.*, South Asia, parts of Latin America, and Eastern Europe) [5].

Although the occurrence of AMI seems to decrease in older populations during the past years, younger men and women presenting AMI have not experienced a similar decline [6]. Several epidemiological studies have underlined the increasing prevalence of AMI among young adults, *i.e.*, <30-40 years old [7], with men exhibiting much higher risk than women [8, 9]. Although cases of young patients with AMI were extremely rare until the early 1940s, in 1947, a series of 50 patients with an AMI younger than 35 years old came to light [8], underlying this upcoming phenomenon. During the forthcoming decades, the clinical features of AMI patients aged under 30 years were described [9]. Lifestyle behaviours, such as smoking, constitute a principal threat for a premature cardiac

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event, while rates of CVDs are influenced by race/ethnicity, socio-economic status (SES) and -aspects [10, 11]. According to the INTERHEART study [12], CHD occurs at a younger age in South Asians, with 25% of all MIs in this population reported to occur below 40 years of age; as South Asians represent approximately a quarter of the world's population, CHD occurrence in this specific population and age-group accounts for >50% of the global CHD mortality [6, 12].

Since an acute cardiac event also carries a significant psychological impact and financial burden for the patients and their families, especially at a young age, there has been considerable interest in elucidating the metabolic and lifestyle causes behind this phenomenon.

Childhood obesity has reached epidemic levels worldwide. According to the Organization for Economic Co-operation and Development (OECD), in 2017, nearly one in six children was overweight/obese [1]. These rates are even more alarming due to the unhealthy lifestyle behaviours children tend to adopt in recent years. Thus, considering the alarming rate of childhood obesity, this narrative review aimed to evaluate whether excess body weight from the early stages of life increases the risk of premature AMI in young adults below 35 years old.

### 1.1. Searching and Appraising the Literature

A comprehensive literature search was carried out using the MEDLINE and Google Scholar databases (MeSH search terms/keywords: childhood obesity, adolescent obesity, young adults, excess weight, heart disease, cardiovascular diseases, coronary heart disease, acute myocardial infarction). The search was restricted to cross-sectional epidemiologic studies, as well as systematic reviews and meta-analyses published in English, investigating AMI occurrence in young patients under 35 years of age and its correlation with their pre-adolescent obesity status. There was no time limit. The authors also considered reference lists in original epidemiological articles and reviews.

Each author independently evaluated the results of the literature research, extracting the most pertinent knowledge. Both authors verified the accuracy and completeness of the extracted information from the selected studies.

### 1.2. Definition of the term "Young" Patient with AMI

There is a disparity in the literature regarding the definition of "young" concerning premature CHD and AMI [13]. In particular, the term "young" varies from ≤35 to ≤55 years of age [14 - 18]. Thus, as there is no universally accepted age cut-off, we considered ≤35 years old as a threshold to define "young" AMI patients.

### 1.3. Reporting the Results of Selected Studies

Exploring the Risk Factors for Premature AMI.

One of the pioneer studies in the field of CVD epidemiology, the Framingham Heart Study (beginning in 1948 in Massachusetts, USA), and with a very long follow-up period of 40 years, was the first to provide substantial insights into the causation of CVD, identifying a set of risk factors, including excess weight [19, 20]. Since then, underlying determinants of CVD encompass several socio-economic and cultural changes (*i.e.*, globalization, urbanization, population aging), along with lifestyle, biochemical, hormonal, mental, hereditary and genetic factors, being acknowledged as other independent or synergistic determinants of CVD occurrence [1], in both sexes, at all ages [21].

It should be noted that for many years, CVD was considered the disease of middle-aged and older men. However, this concept is now characterized as a simplistic misconception since many epidemiologic studies have reported that AMI also occurs in much younger individuals [22, 23]. Moreover, it is now well understood that the establishment of CVD risk factors is a progressive process that begins during the early stages of life, consolidated in childhood, tracks and expands into adulthood, leading to a high risk of acute coronary events among young individuals [18, 23, 24].

The risk factor profile among young AMI patients mainly encompasses cigarette smoking (and, nowadays, electronic-cigarette use, too), adherence to unhealthy diets, physical inactivity, and obesity, which lead to excess blood lipids levels, arterial stiffness, high blood pressure, and, consequently, the development of atherosclerosis [18 - 24]. Among the cluster of risk factors in young AMI patients, obesity plays a significant role [21, 25, 26]. The relationship between obesity and atherosclerosis was thought for many years to be indirect [27] and dependent on other CVD risk factors, including hyperlipidemia, hypertension, and diabetes [28]. However, recent long-term, longitudinal studies [1, 29] have demonstrated that obesity is also an independent risk factor for coronary atherosclerosis.

The Framingham Heart Study was one of the first which highlighted that the age-adjusted relative risk for CVD increased among overweight and obese men and women. The study's investigators reported that obese people exhibit earlier pathologic evidence and higher relative risk (RR) for CVD and experience an AMI event at earlier stages of life [19]. In addition, according to the more recent large-scale INTERHEART Case-Control Study (2004), which evaluated the effect of various factors associated with AMI in patients from 52 countries, obesity increased the risk of AMI in all patients regardless of age, sex, and population regions [21]. Another study focused on Asian populations, the Kailuan study, which is a population-based cohort study (June 2006-October 2007) involving residents of the Kailuan community in Tangshan City of China comprising 101,510 participants [30], demonstrated that metabolically healthy obese subjects showed a substantially higher risk of AMI, even premature, compared with normal-weight subjects [31]. In line with the aforementioned studies, several meta-analyses have also suggested a significant association between obesity and the incidence of AMI [32]. On top of all these findings, the American Heart Association (AHA), the European Society of Cardiology, the World Health Organization, and several other health organizations have classified obesity as a major, modifiable risk factor for CVD [1 - 4].

### 1.4. Epidemiology of Childhood Obesity

Increased childhood obesity is acknowledged as one of the

modern era's main challenges for public healthcare. According to the most recent estimates [33], childhood obesity and overweight have increased substantially over the past four decades. In particular, the WHO estimates that in 2020 there will be 39 million children under five years of age who are overweight or obese. Moreover, the prevalence of obesity among those aged 5-19 years has increased from <1% globally in 1975 to 6% of girls and 8% of boys in 2016 [34]. The number of obese children and adolescents (aged 5-19 years) is predicted to rise to 254 million by 2030, according to projections by the World Obesity Federation using data from the Non-Communicable Disease Risk Factor Collaboration (NCD-RisC) [35]. Given the global emergency posed by excess weight in children, member states of the WHO endorsed "no increase in childhood overweight by 2025" as one of the six global nutrition targets in the 'Comprehensive Implementation Plan for Maternal, Infant and Young Child Nutrition' [36].

### 1.5. Childhood and Adolescent Obesity as a Risk Factor for Premature AMI

Although the effect of childhood obesity on body weight status at later ages has now been well established [33], childhood obesity as a factor that may predispose later development of CVDs among young patients has not been well understood and appreciated. As childhood obesity persists in adulthood [37, 38], recent studies have supported that a rise in children's Body Mass Index (BMI) contributes to the risk of developing a variety of CVDs [39]. Taking into account that children have started developing diseases that were conventionally considered "adult" conditions [40], there is an apprehension about the increasing rates of obesity in children that may lead to an AMI at a younger age [41].

The first epidemiologic evidence identifying children developing multiple CVD risk factors and the early onset of AMI comes from the Bogalusa Heart Study in the late 1990s [42]. The study included school children aged 5-14 and pre-school children aged 2.5-5.5 years. Approximately 60% of overweight 5-10-year-old children had at least one CVD risk factor, such as high blood pressure, hyperlipidemia, or elevated insulin levels [43]. From the same cohort of 5-10 year-olds, >20% of overweight children had two or more CVD risk factors, substantially increasing their risk for earlier CVD [43]. The study also revealed the association between childhood BMI and adult AMI risk in children aged ≥12 years, which was approximately equivalent to an 11% increase in the risk of per $kg/m^2$ increase in BMI [40]. In a more recent study enrolling overweight children aged 1-17 years, their overweight status increased the odds for prehypertension by 50% and even doubled or tripled the odds of hypertension compared with normal-weight children [44]. Similar risks of future AMI events were also noted in a study of 7-13-year-old Danish children [38]. More recently, Guzzetti *et al*. [45] enrolled 1,409 obese children and adolescents (646 boys, median age 9.7 years, range 2-18 years) referred to the Endocrine Unit between 2000 and 2016. Cardiovascular risk factors (CVRF) were already established at a pre-pubertal age. Furthermore, the prevalence and severity of CVRF in children and adolescents with obesity were influenced by gender and pubertal status.

In a systematic review and meta-analysis published in 2012, including 63 studies and 49,220 school-aged children [46], the authors reported a substantial worsening of CVD risk profile in overweight and obese school-aged children. As an example of the gradient effect of increased BMI on risk parameters for CVD, the mean difference in systolic blood pressure between normal and obese children was 40% higher than for normal and overweight children.

Concerning the risks of premature AMI in adolescents, the Muscatine Study in the late 1990s [47], conducted in Muscatine, Iowa, evaluated young adults (n=197 men and 187 women between the ages of 20 and 34 years) with CVD risk factor profile measured during their childhood. This study reported that increased weight during childhood was the strongest predictor of coronary calcium later in life. In turn, coronary calcium is a marker for plaque formation in the coronary arteries and is associated with an increased risk of AMI. In line with previous findings, a more recent longitudinal study conducted in 2016 among Israeli adolescents (mean age, 17.3±0.4 years) [48] reported that childhood obesity was associated with a 2-fold increase in CVD morbidity and mortality by the age of 47-57 years. Finally, a meta-analysis of 37 studies, published in 2016, including children and adolescents aged between 12 and 18 years [40], showed that a 1-standard deviation increase in BMI during childhood and adolescence (*i.e*., ages 7-18 years) was associated with a 14-30% increase in the risk of adult AMI. Additionally, a positive association was shown between BMI during childhood and adult CHD. In particular, an approximate 10% increase in the risk of CHD per $kg/m^2$ increase in BMI was observed. Moreover, weight status was a significant predictor of future morbidities; specifically, it was observed that among children and adolescents with excess body weight at baseline, approximately 31% of them at follow-up developed diabetes, 16% developed stroke, 22% developed hypertension, and 20% developed CHD at middle age, *i.e*., between 40-55 years old [40].

From a mechanistic, pathophysiological point of view, it has been suggested that the earliest structural lesions of atherosclerosis, *i.e*., fatty streaks, can be detected in young children [49]. Accumulation of lipid-laden macrophages, monocytes, and T-cells is followed by platelet aggregation, vascular smooth muscle cell proliferation, and the formation of a lesion capped by smooth muscle and collagen (fibrous plaque) [22]. Besides an altered metabolic profile, various adaptations/alterations in cardiac structure and function occur in the individual as adipose tissue accumulates in excess amounts, even without comorbidities. Hence, excess body weight, especially from a young age, may affect the heart through its impact on recognized risk factors, such as dyslipidemia, hypertension, glucose intolerance, inflammatory markers, obstructive sleep apnea/hypoventilation, and the prothrombotic state, in addition to as-yet-unrecognized mechanisms. Moreover, in the Guzzetti *et al*. study, impaired insulin resistance and dyslipidemia were the most commonly diagnosed CVRFs in pre-school children (≤6 years). Moreover, pubertal progression was associated with an increase in the hypertension rate in both males and females [45].

The association of obesity with accelerated atherosclerosis has been underscored by the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study [50]. Briefly, in 3000 individuals aged 15-34 years, a significant correlation was observed, especially in young men, between obesity and fatty streaks, raised lesions in the right coronary artery, stenosis in the left anterior descending artery and stenosis in the left anterior descending artery, with the possible risk of AMI. Independent pathologists evaluated lesions after microscopic examination of appropriately stained specimens [51].

Additionally, other atherosclerotic-related biochemical markers in children and adolescents, such as serum uric acid (SUA), and its correlation with the risk of occurring CVD events have been highlighted in recent epidemiological studies [52, 53]. Further exploration of the link of SUA with overweight and obesity in children was presented in a recent study among obese Danish children and adolescents (n=171, 4-18 years old) [54]; according to the findings, children who achieved a weight reduction had a significant reduction in SUA and vice versa.

Lastly, childhood obesity seems related to increased CVD risk due to its association with atherogenic lipid profile, as expressed with an increased triglyceride/high-density lipoprotein cholesterol ratio observed in obese children [55].

All the aforementioned findings highlight that weight, especially obesity, has a substantial effect on the risk parameters for CVDs present in children. This effect could give them a head start compared to their normal and overweight classmates for future CVDs [46].

### 1.6. Reversing Synergistic Obesity and Lifestyle-related Patterns Linked with Premature AMI

It is now strongly supported that a vital challenge for public health is to reverse the health consequences of childhood obesity. A large body of scientific evidence has emphasized the importance of dietary habits, concluding that promotion of healthy eating from every stage of life, *e.g.*, in pre-school children, may significantly reduce the risk of CVD, underlying that - among all, the conventional lifestyle-related CVD risk factors – *i.e.*, dietary habits -, maybe the most significant discriminating factors for premature AMI [56, 57]. The beneficial synergistic effect among the nutrient-rich foods included in a healthy dietary pattern and its positive impact on later cardiometabolic risk has already been highlighted in the epidemiology of childhood obesity and CVDs [42, 43, 58, 59].

It should also be underlined that the need for reversing premature CVD risk factors in children, like obesity, also highlights the role of family, and education, as a public health priority [60 - 62]. Health Literacy (HL) has dynamic and important interfaces with CVD prevention, recognition, management, and treatment [63], mainly when CVDs occur prematurely - as previously discussed - at young ages. The positive role of adequate HL in CVD prevention has been well documented [64], reporting that poor HL could be implicated in the aetiology of obesity and could act as an essential cause behind obese people's inability to encounter difficulties in overcoming obesity issues. Understanding health information has been inversely associated with underweight and obesity, general health status and behaviour [65].

## CONCLUSION

Obesity in children is becoming a worldwide pandemic that requires urgent and immediate attention and action. There is an emerging need to adopt a multidisciplinary approach involving dietary, physical, and behavioural strategies, policies, and interventions targeting the reduction in premature morbidity due to non-communicable diseases, like obesity, to promote cardiovascular health, quality of life, and longevity. This narrative review brought to light major public health concerns about the overall health experience of those who develop obesity early in life. Moreover, questions were raised about the understudied issue of whether the impact of the obesity epidemic in children might shorten the life span of the next generation due to its association with the premature advent of CVD morbidity. Undoubtedly, the burden of CVD will dominate our practice of medicine this century. Given the multifactorial nature of this complex disease process and the continued development of new treatment regimes, accurate monitoring of epidemiological data will be essential to record trends in morbidity and mortality over the foreseeable future.

## LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| **AMI** | = | Acute Myocardial Infarction |
| **CVD** | = | Cardiovascular Diseases |
| **GBD** | = | Global Burden of Disease |
| **BMI** | = | Body Mass Index |
| **WHO** | = | World Health Organization |

## CONSENT FOR PUBLICATION

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## CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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