CHILDHOOD OBESITY AND ITS IMPACT ON YOUNG ARTERIES

PhD THESIS

Andrea Emese Jakab MD

Consultant: Csaba Bereczki MD PhD

Clinical Medical Sciences Doctoral School

Program Director: Prof. Lajos Kemény MD DSA

SZEGED

Department of Pediatrics, Faculty of Medicine

University of Szeged

2018
PUBLICATIONS DIRECTLY RELATED TO SUBJECT OF THE THESIS:


ABSTRACTS


ABSTRACT ON OTHER TOPIC:
"...the individual has now passed forty years, perhaps fifty years of age, his lungs begin to degenerate, he has a cough in the winter time, but by his pulse you will know him."

F. A. Mohamed, 1879

Introduction

Childhood obesity

According to the World Health Organisation (WHO), overweight and obesity are defined as abnormal or excessive fat accumulation that presents a risk to health. A crude population measure of obesity is the body mass index (BMI), a person’s weight (in kilograms) divided by the square of his or her height (in metres). An adult person with a BMI of 25 is generally considered overweight, with a BMI equal to or more than 30 is considered obese. Obese class I means that BMI is between 30.00–34.99, in obese class II the BMI is between 35.00–39.99 and finally, obese class III are patients with BMI equal to or above 40.00. For children under 5 years of age: overweight is weight-for-height greater than 2 standard deviations (SD) above WHO Child Growth Standards median; and obesity is weight-for-height greater than 3 SD above the WHO Child Growth Standards median. Overweight and obesity are defined as follows for children aged between 5–19 years: overweight is BMI-for-age greater than 1 SD above the WHO Growth Reference median; and obesity is greater than 2 SD above the WHO Growth Reference median [1]. World Obesity / Policy & Prevention (formerly International Obesity Task Force or IOTF) has adapted adult BMI cut-off values (16, 17, 18.5, 25, 30 and 35 kg/m²) to child centiles [2], which is easy to derive and they can be expressed as BMI centiles. It is more useful in paediatric population, because WHO standards (due to its construction method) are relatively low in young patients and high in older subjects [2].

Prevalence of overweight and obesity in the World

The increasing number of overweight and obese children and adolescents has become a serious and alarming phenomenon worldwide. Between 1980 and 2013, the prevalence of overweight and obesity increased from 10% to 12.7% in the population aged 2–19. This rate is even worse in the industrialised countries: during the period analysed, the prevalence increased from 16.9% to 23.8% in boys, and from 16.2% to 22% in girls [3]. As it is shown in Figure 1–2, between 1975 and 2016, the mean BMI raised in boys, as well in girls worldwide.
The pace of the increment is alarming, in cc. 40 years the prevalence increased from 10 million to more than 70 million in boys in the Central and Eastern Europe region, and from 10 million to 50 million in girls in the same region [4].

The epidemic of overweight and obesity has intensified the pace of research, in order to identify the possible reasons and the harmful consequences of this conditions not only in childhood, but in adults as well.

**Etiology of childhood obesity**

Obesity is subdivided in two subgroups: exogenous and endogenous [5]. Endogenous may be caused by different endocrine malfunctions, genetic or syndromic causes; whereas exogenous could be resulted from the imbalance between energy intake and expenditure, or from medications (e.g., glucocorticoids, tricyclic antidepressants), or even from impaired metabolic programming [5]. Considering the fact, that the target population of this research were
children with exogenous obesity, the following part of the thesis will give a summary about this subgroup.

Although researchers have took efforts to explore the genetic factors and molecular background of the individual susceptibility to obesity, these findings cannot explain the obesity epidemic entirely. Genes of the human body have not changed substantially during the past decades. Promotions of the obesogenic behaviour is responsible for obesity nowadays. Gaining weight in this increasing obesogenic environment is very easy for children, while it requires sustained efforts remaining fit and healthy [6]. Contributing environmental factors for increased BMI could be divided into three subgroups. Firstly, individual behaviours such as unhealthy dietary habits including the consumption of energy dense food, large portion sizes and excessive snacking [7], reduced sleep time resulting from increased screen time [8], lack of regular physical activity or sedentary lifestyle. Secondly, to micro-environmental factors belong family (parenting styles and different patterns of diet and physical activity, smoking and alcohol consumption influence the child’s choices) [9,10] school (lack of healthy lifestyle education, sport facilities, unhealthy lunches) [11,12] and neighbourhood (playgrounds, closeness of healthy food groceries) [13–15]. Thirdly, macro-environmental factors are food industry - which have an impact on the risk of obesity with the production, marketing and advertising of high fat and sugar containing foods - and government, which should provide a healthy environment for children and should follow a strict, restrictive policy aiming the reduction of the availability of unhealthy snacks [7,16]. Considering the highlights of the literature, we may conclude to the possible solution: we must “cure” environment first, to combat the alarming increase of obesity [6].

**Consequences of childhood obesity**

Medical researchers have long recognized that being overweight or obese carries many serious health risks for adults [17]. The question rises, whether children face the same range of risks as adults or they form an exceptional group. Several conditions, thought to be only applicable in adulthood are now being represented in youth, moreover, they are becoming more frequent than before. Children are more vulnerable to obesity-related diseases, because their bodies are in a growing and developing phase. Overweight or obesity are not merely an aesthetical issue for the individuals, but consequences of this condition having an adverse, either immediate or long-term effect on their health. These obese children are more prone to have early atherosclerosis [18], hypertension [19] or diabetes mellitus [20] as adults.
Moreover, this condition may also result in insulin resistance [21], metabolic syndrome [22], dyslipidaemia [23], it may contribute to obstructive sleep apnoea [24]; furthermore, non-alcoholic fatty liver disease [25], gastroesophageal reflux [26], tibia vara (Blount disease) [27] may also be developed, or even psychic condition may be affected (depression) [28].

**Obesity related cardiovascular morbidity and mortality**

The cardiovascular system consists of a dynamic series of conduits, which are vulnerable to many illnesses that may result in heart attack – in the case of heart arteries – or in stroke – in the case of cerebral arteries. These processes make the heart also assailable to thickening of the heart muscles resulting in diminished function [29].

**Hypertension**

Overweight and obesity are main contributing factors to develop hypertension not only in adulthood but in childhood, as well [30]. Figure 3 illustrates, that there are factors simultaneously attenuating and stimulating the development of high blood pressure in overweight adolescents [31].

![Figure 3](image)

**Figure 3** Factors associated with the development of hypertension in overweight adolescents. Original Figure from Kelly and her co-workers [31]

**Note:** *Denotes studies that present effective estimates in adolescents only.

**Abbreviations:** ACE I/D; angiotensin converting enzyme insertion/deletion, CRP; C-reactive protein, eNOS; endothelial nitric oxide synthase, HDL; high-density lipoprotein, HOMA-IR; homeostasis model assessment-estimated insulin resistance, IGF2; insulin-like growth factor, LDL; low-density lipoprotein, NT-proBNP; n-terminal pro-brain natriuretic peptide, Y2R, Y2 receptor.
Recent studies have found that the odds for hypertension are 2.5 to 3.7 times higher in children with overweight depending on their race and sex [32]. Consequently, the higher is the frequency of children with overweight or obesity, the higher is the portion of children suffering from hypertension [33].

**Left ventricle hypertrophy**

Uncontrolled high blood pressure - resulting in an increased load - forces the heart to provide increased effort to pump blood via the aorta in to the rest of the human body. This process may lead to thickening of the main pumping chamber, to left ventricle hypertrophy. Similarly to hypertension, left ventricle hypertrophy also shows a strong correlation with increased BMI in childhood [34]. Researchers have found, that the reason for this could be that the development of the heart follows the development of the body composition [35]. This suggests that in a body with excessive amount of fat tissue, the left heart chamber should thicken itself ultimately. Subsequently this hypertrophy could lead to increased risk for heart attack, so it may raise the risk for future cardiovascular morbidity and mortality already in young population.

**Atherosclerosis**

Hardening of the arteries is a progressive condition, called atherosclerosis, which starts with a fatty streak on the inner layer of the vessel (endothelium), and it is followed by a fibrous plaque leading to a blockage in the blood flow. Due to the lack of non-invasive techniques to detect atherosclerosis at the early stage, it was not clear, whether obesity influences atherosclerosis or it affects youth as well as adults. PDAY study [36] and Bogalusa study [37] helped to clarify the prevalence of atherosclerosis in young adults and the connection between obesity and atherosclerosis. In the PDAY study autopsy was used to identify lesions on the surface of the arteries in subjects who died of accidents, murders or suicides, hypothesized that they were “healthy” subjects, not suffering from any disease at the time of the death. This working group described, that atherosclerosis begins already in youth, and the prevalence of fatty streaks and clinically significant lesions raises suddenly in the 15 to 34 year age span.
Table 1: Prevalence of atherosclerotic lesions in subjects from the PDAY study. Copy from the original article [36].

<table>
<thead>
<tr>
<th>Age, y</th>
<th>No. of Cases</th>
<th>Thoracic Aorta</th>
<th>Abdominal Aorta</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases</td>
<td>Fatty Streak</td>
<td>Fibrous Plaque</td>
</tr>
<tr>
<td>15-19</td>
<td>210</td>
<td>3.3</td>
<td>0.5</td>
</tr>
<tr>
<td>20-24</td>
<td>253</td>
<td>3.6</td>
<td>0</td>
</tr>
<tr>
<td>25-29</td>
<td>295</td>
<td>9.8</td>
<td>0</td>
</tr>
<tr>
<td>30-34</td>
<td>250</td>
<td>21.2</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Table 1 shows the prevalence of several types of lesions (fatty streak, fibrous plaque, complicated, calcified) found in the PDAY study. Surprisingly, the prevalence of fatty streaks was 100% in white and black subjects. In the age group 15–19 years a total of 13.1% white men and 6.8% of white women suffered from fibrous plaque in the abdominal aorta, and 3.3% of white men and 1.5% of white women suffered from fibrous plaque in the thoracic aorta. Bogalusa study identified with the help of antemortem analysis the possible link between elevated BMI and early atherosclerosis [37]. These results demonstrate the presence of atherosclerosis even in children at very young age and the harmfulness of increased BMI on the cardiovascular system. Health professionals should bear in mind that atherosclerosis starts decades earlier before having clinical manifestation, already in childhood, moreover overweight and obesity are significantly related to the atherosclerotic lesions. The question rises, how can we measure the progress of atherosclerosis in humans, especially in children?

Measurements of arterial function parameters

Non-invasive assessment of arterial function parameters in adults is getting more common among health care professionals, to perform proper risk stratification for cardiovascular...
morbidity, furthermore to measure possible target organ damage in patients. Moreover, it is strongly suggested to measure these parameters as it was recommended by the relevant guideline [38].

Featuring parameters of arterial function include aortic pulse wave velocity (PWV_{ao}), aortic augmentation index (Aix_{ao}), central systolic blood pressure (SBP_{ao}), and central pulse pressure (PP_{ao}). Each previously mentioned parameters are considered as strong, independent predictors of mortality and morbidity of CVD in adulthood [39–41].

**Arterial stiffness – aortic pulse wave velocity (PWV_{ao})**

Arterial stiffness is a dynamic feature of great arteries and this is determined by 3 factors: the structure of the vessel, the arterial function and by the actual blood pressure [42]. O’Rourke has found, that the invasively measured pulse wave pressure - resulted from the ejection of the left ventricle - travels down via the ascending aorta (Figure 4) [43].

![Figure 4](image)

**Figure 4** Exposure of the aortic pulse pressure from the level of the aortic valve [43]

During this measurement they recorded the onset of the pulse pressure in the aorta in every 5 centimetres descending from the level of the aortic valve. As it is marked in the picture (red arrows) the further the catheter was from the aortic valve, the later was the onset of the pulse pressure obtained. Knowing the distance taken by the pulse pressure (in this case s=0.45 m), and the time needed to cover this distance (t=0.067 sec), velocity can be calculated by
dividing the distance with the time (PWV_{ao} = 6.7 \text{ m/s}). PWV_{ao} in healthy subjects is ranged between 3.9±6.5 m/s depending on the parts of the aorta (ascending, thoracic, abdominal).

Ageing is associated with an inevitable process, during which the main component of the aortic wall (elastic fibres) fragmentates and is replaced by the one-hundred times stiffer component, called collagen [44]. Half-life of the elastin is around 45–50 years [45]. Consequently, PWV_{ao} increases simultaneously with ageing even in healthy individuals. To put in other words, the stiffer the arteries, the faster the PWV [46–48]. In the case of atherosclerosis, the process of arterial stiffening is accelerated, therefore the PWV_{ao} shows marked increase [49] in these cases.

*Nilsson and his co-workers* have conducted “EVE and ADAM” research [50], in which they have assumed that “the arterial stiffness is a cumulative measure of the damage effects of CV risk factors on the arterial wall with aging” (Figure 5).

According to Nilsson’s theory, “circulating” biomarkers (e.g., blood pressure, blood sugar level, C-reactive protein level or blood lipids) give merely a “snapshot” about the actual condition of the patient’s circulatory system, however, these markers do not reflect properly the cumulative damage on the aortic wall the patient got during lifetime, including effects of all identified and non-identified “circulatory” risk factors. Therefore, measurements of “tissue” biomarkers, such as PWV_{ao}, SBP_{ao}, cIMT and endothel function play an essential role in risk stratification for cardiovascular diseases. Measurement of arterial stiffness may avoid
patients being mistakenly classified as at low or moderate risk when they actually have an abnormally high arterial stiffness, placing them within a higher risk group [51].

What do we know about PWV in the youngest? Researches have proved the deterioration of the arterial function in children in diverse type of diseases, such as in early atherosclerosis [52], obesity [53], familiar hypercholesterolaemia [54], diabetes mellitus type I. [55], juvenile hypertension [56], congenital heart diseases [57], end stage renal diseases [58], HIV infection [59], Kawasaki disease [60], neurofibromatosis [61], vasculitis [62], extreme prematurity [63], very low birth weight [64], primary snoring [65], bronchial asthma [66], cystic fibrosis [67], hematopoietic stem cell transplantation [68], hypertriglyceridemia [69].

However, it was complicated to assess these parameters in a very young population due to the old-fashioned techniques [42]. Today, with new methods we can provide data on a large paediatric population. Hidvégi and her co-workers have evaluated normal values of PWV in a large (n=3,374, 1,802 boys), healthy population [70].

Figure 6 Smoothed percentile curves from third to 97th of aortic pulse wave velocity (PWV\textsubscript{ao}) related with age for boys (a) and girls (b). Copy from the original article [70].

Figure 6 demonstrates the percentile curves of PWV\textsubscript{ao} in children. We can observe, that the 50\textsuperscript{th} percentile curve shows an uneven increasing with ageing, however, PWV\textsubscript{ao} values do not alternate between the ages of 3 and 8, afterwards it rises markedly in both sexes. In this study, they have found that between 3 and 18 years in boys PWV\textsubscript{ao} rises from 5.5±0.3 m/s to 6.5±0.3 m/s, and in girls it rises from 5.6±0.3 m/s to 6.4±0.3 m/s, without significant difference between boys and girls.
Augmentation index (Aix\textsubscript{ao})

Generated and ejected by the left ventricle, the early systolic pulse pressure wave (P\textsubscript{1}) travels down via the aorta and is reflected by the aortic bifurcation (P\textsubscript{2}) (see Figure 18) during the systolic phase, otherwise it “augments” on the P\textsubscript{1}. Aix is the pressure difference between the P\textsubscript{2} and the P\textsubscript{1} pressure divided by the late systolic peak pressure. Augmentation index is an indirect marker for arterial stiffness, it refers to the total peripheral vascular resistance (TPVR) [71], regulated by resistance vessels (i.e., small arteries, arterioles). Soltész and his co-workers performed a study, in which they have measured Aix, flow-mediated dilatation (FMD) and common carotid intima media thickness (ccIMT) in patients with autoimmune diseases. Although, both Aix\textsubscript{ao} and PWV\textsubscript{ao} showed significant correlation with FMD, Aix demonstrated a stronger correlation with FMD, suggesting this parameter do not refer to arterial stiffness [72]. Aix\textsubscript{ao} varies among healthy patients depending on the actual physiological state of the human body. Ageing is associated with the increase of the Aix\textsubscript{ao} [42], however, raising TPVR is not the reason for that, but the natural ageing of the aortic wall leading to stiffening, raises the PWV. Due to the velocity elevation, the pulse wave pressure returns in shorter time (return time shortens), therefore the second wave returns and augments earlier (on a higher point) to the descending part of the first wave, resulting in a higher amplitude of the second wave, otherwise the Aix increases.

Interestingly, Aix is elevated in very young children, similarly to the Aix in adults with different types of diseases [73–75]. Majority of the authors hypothesize that the reason for this is the shorter upper body of children, resulting in shorter length of the aorta. Therefore, the reflected or second pulse pressure wave returns earlier to the aortic root, which leads to an earlier augmentation on the early reflected pulse pressure wave, causing with this an increased Aix (Figure 7).
Figure 7 Original arteriograms of pulse pressure curves in a 3-year-old boy (a) and 17-year-old boy (b).

Figure 7 demonstrates, that ejection time is almost identical in case a and b, the difference lies on return time, because it is 115 msec in the 3-year-old patient, whereas it is 135 msec in the 17-year-old patient. Consequently, the reflected wave returns earlier and on a higher point of P₁, and the Aixₐₒ will be 32.22% in case a, and -2.85% in case b. Studying the relation between age and Aixₐₒ, invasive investigation was performed by Murakami and his co-workers in 2010 (Figure 8) [76].

Figure 8 The relationship between augmentation index and age. Copy from original article [76] combined with the results from Hidvégi’s publication [77].
In this research 61 patients aged 0−30 years had undergone cardiac catheterization for left-to-right shunt disorders to determine reference for the aortic augmentation index. They have found, that Aix is increased in the early ages and it starts to decrease afterwards. Until recently, this phenomenon was not proven directly, but indirectly, because there was a lack of return time data correlated with age and height in children, which could verify this theory. Hidvégi and her co-workers have published the normal values for Aix and RT in children and adolescents [77] (Figure 9). They have established, that RT is significantly shorter in the early ages of childhood than in puberty -during which height of children will be longer by cc. one meter-, and RT increases proportionally with height. Subsequently, we might consider this hypothesis directly proven.

![Figure 9](image-url) Smoothed percentile curves from 3rd to 97th of Aix\textsubscript{ao} and return time in boys (a, c) and girls (b, d). Copy from original article [77].

Furthermore, differences between sexes have been discovered too. Aix\textsubscript{ao} was higher in girls than in boys between the age of 14–18. RT was found to be higher in boys from the age of 13 and thereafter. Moreover, the main tendency of the changes (Aix\textsubscript{ao} decrements, RT rises linearly in childhood, and both decelerate at the beginning of puberty) was similar in both genders, but the onset of the changes was different, it could be due to the different onset of puberty in boys and girls [77].
Central and peripheral blood pressure – \( SBP_{ao} \) and \( SBP_{brach} \)

O’Rourke and his co-workers have invasively measured the pressure is the aorta and in the brachial artery simultaneously, they have found that the pressure in the brachial artery is markedly lower, than in the aortic root (Figure 10) [78].

![Pulse pressure curves simultaneously recorded by invasive catheters located in the brachial artery and in the aortic root. In the upper part of this figure is the ECG record in the lead II of the patient [78].](image)

Possible cause of this phenomenon is that the brachial artery consists of smooth muscle cells, while the aorta is basically built up of elastic fibres (Figure 11). Large arteries - such as aorta - are not simply passive conduits but also serve to buffer the marked changes in pressure resulting from the intermittent ventricular ejection, consequently, maintaining a standard pressure even in diastolic phase to enhance coronary and peripheral blood flow. To achieve this, aorta should be compliant, thereby storing a relevant proportion of blood ejected from the left ventricle and thereafter releasing it during diastole. Therefore, aorta firstly dilates, and the pressure increases moderately, whereas in the muscular type arteries (e.g. brachial artery) the loading pressure increases markedly due to the lack of elastic fibres and the substantial proportion of smooth muscle cells.

![Histology of the aorta and muscular type artery [79].](image)
As a result, while the mean arterial pressure (MAP) in the circulatory system is mainly steady, the pulse pressure increases gradually from the level of the ascendant aorta towards the periphery, this is called pulse pressure amplification, which has been proven and explained [78] by O’Rourke (Figure 4). In a healthy, young adult, where the aortic wall is flexible, \( \text{PWV}_{\text{ao}} \) is within the normal range, the amplitude of the reflected wave should be markedly lower than the amplitude of the first wave. Nevertheless, in a healthy patient the aortic wall is “getting older” too, during which process the flexible elastic fibres will be replaced with collagen tissue [44]. Resulting from this natural ageing, aortic wall becomes stiffer and more rigid, \( \text{PWV}_{\text{ao}} \) increases, reflected wave returns earlier to the aortic root and augments earlier on the first wave, leading to the modification of the central pressure curve causing with this increase of the central systolic blood pressure, which enhances the risk for stroke or left ventricle hypertrophy due to the increased afterload of the left chamber.

Today, high blood pressure is determined by \( \text{SBP}_{\text{brach}} \) according to the relevant guidelines [38]. Majority of physicians and general practitioners do not know the conception and importance of central or aortic systolic blood pressure. This could be resulting from the complex measuring methods of \( \text{SBP}_{\text{ao}} \). On the other hand, several studies have recently demonstrate the leading role of \( \text{SBP}_{\text{ao}} \) in the CV mortality [41,80–82]. Arteriograph provides simultaneous measurement of \( \text{SBP}_{\text{brach}} \) and \( \text{SBP}_{\text{ao}} \), supplying important parameters to the physician about the patient in clinical practice. Until recently, there was a lack of data about the normal values of central or aortic systolic blood pressure in children, but Hidvégi and her co-workers have also evaluated the normal \( \text{SBP}_{\text{ao}} \) percentile in children and adolescents [83].

![Smoothed percentile curves from 3rd to 97th of SBP_{ao} in boys and girls. Copy from original article [83].](image)

**Figure 12** Smoothed percentile curves from 3rd to 97th of SBP\(_{\text{ao}}\) in boys and girls. Copy from original article [83].
Figure 12 demonstrates that neither SBP<sub>ao</sub>, nor SBP<sub>brach</sub> show linear increase with ageing in children. In boys, between the ages of 3 and 10 SBP<sub>ao</sub> remains constant, afterwards it rises gradually. In girls, the constant phase lasts until the ages of 11, after this it increases similarly like in boys, and at the age of 15 it becomes steady again. SBP<sub>ao</sub> rises from 96.8±7.1 mmHg to 110.1±7.3 mmHg in boys between the ages of 3 and 18, whilst in girls from 97.5±7.8 mmHg to 105±7.5 mmHg. After the age of 16, SBP<sub>ao</sub> is significantly lower in girls.

**Non-invasive assessment of arterial function**

Mainly, 3 distinct types of method were used to assess arterial function: applanation tonometry (SphygmoCor, AtCor Medical, Sydney, Australia), piezoelectric method (Complior, Artech Medical, Pantin, France), and flow assessment by Doppler-sonography. Only applanation tonometry measures all the main arterial function parameters (PWV, Aix, SBP<sub>ao</sub>). Comparison of the devices are shown on Table 2.

**Table 2** Summary of main advantages and limitations of three different techniques for arterial stiffness. Copy from original article [84]

<table>
<thead>
<tr>
<th>Device</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Compilir     | - The delay in pulse transit time between two arteries is taken simultaneously using a 'foot to foot' waveform method  
- Numerous data on the prognostic value of c-f PWV so obtained are available | - Operator's skill dependency  
- Carotid tonometry is difficult  
- Necessity to undress and expose the groin  
- Possibility of technical errors in obese patients  
- Uncertainty and approximation in measurement of distance between the two arteries  
- Theoretical risk of carotid plaque rupture by probe (never reported)  
- Patients with atrial fibrillation cannot be evaluated  
- Unable to allow PWA  
- Underestimation of elevated PWV by built-in algorithm  
- Carotid tonometry is difficult  
- Necessity to undress and expose the groin  
- Possibility of technical errors in obese patients  
- Uncertainty and approximation in measurement of distance between the two arteries  
- Theoretical risk of carotid plaque rupture by probe (never reported)  
- Patients with atrial fibrillation cannot be evaluated  
- Debate regarding the validity of the generic transfer function used  
- Need of a precise BP calibration for PWA, currently not available  
- The PWV transit time delay is calculated using reference ECG signals obtained at different times, respectively, for carotid and femoral pulse waveforms sequentially recorded  
- Scarcity data on its validation and on the prognostic value of parameters so obtained are available  
- Patients with atrial fibrillation or marked bradycardia cannot be evaluated |
| SphygmoCor   | - PWA is available allowing assessment of augmentation index and central BP through a transfer function application  
- Numerous data on the prognostic value of the parameters so obtained are available |  |
| ArterioGraph | - The technique only needs access to the patient's upper arm (no need to undress)  
- It is based on an easy methodology (largely operator-independent method)  
- It is a time-saving method. This last assessment of arterial stiffness parameters is particularly suitable to population studies  
- Higher reproducibility of parameters, as compared with the other two methods  
- Potentially adaptable to ambulatory arterial stiffness assessment |  |
Aims

1. To determine the prevalence of overweight and obesity in a healthy population aged 3–18 in Szolnok city and the surrounding area.

2. To observe if there have been any changes in the prevalence of overweight and obesity from the data measured previously in Hungary.

3. To answer what trends can be seen in the changes regarding the prevalence of overweight and obesity in Hungary.

4. To discover if there is a difference in age and sex distribution regarding the prevalence of overweight and obesity.

5. To compare AFPs (PWV\textsubscript{ao}, Aix\textsubscript{ao}, SBP\textsubscript{ao}) in overweight and obese patients with healthy controls in population of wide age range (3–18 years).
Materials and methods

Subjects

6,824 subjects (3,673 boys) aged 3–18 years were recruited from elementary, primary and high schools in Szolnok town (Hungary) between 2012 and 2016. To assess the prevalence of OW and O we have included all data from the investigated population. To set up a correct method for AFPs analysis, from this group we have involved children with OW/O (n=1,363). Subjects with elevated brachial systolic and/or diastolic blood pressure (≥95th percentile related age and sex and height) using by the relevant guideline [85], were excluded from this study. Finally, 719 subjects (431 boys) fulfil the inclusion criteria. Controls have been chosen by identical peripheral systolic blood pressure, age and height. All the subjects were Caucasian with no any chronic diseases and they were not on any regular medications. Informed consent for the measurements was asked for from the parents of the subjects. The protocol was reviewed and approved by the local Institutional Ethics Committee of the University of Pécs, Pécs, Hungary.

Methods

Height and weight measurements were performed in accordance with the Hungarian professional rules [85], using a Kern MGB 150K 100type personal scale and a MSF 200 type mechanical height rod (Kern & SOHN GmbH, Germany). The subjects were categorised by their body mass index (BMI) into normal weight, overweight and obese groups regarding their age and sex, as well [2].

Arteriograph

Arteriograph is a newly developed, non-invasive occlusive-oscillometric device (Tensiomed Kft., Budapest, Hungary). It is composed of a laptop, oscillometric equipment and a series of upper arm cuffs. AFPs were measured by Arteriograph. Validations and the detailed method of the device have been published previously [86,87]. Briefly, the method of the device is based on the physiological fact that the early systolic pulse pressure wave (P₁) generated by the left ventricle travels via the aorta and is reflected from the level of the aortic bifurcation and comes back to the aortic root and augments as a second or reflected wave to the first wave even in the systole (P₂) (Figure 13).
The travel time of the aortic pressure wave from the aortic root to the aortic bifurcation and to back is equal to the time between $P_1$ and $P_2$ (return time, RT). By measuring the distance between the sternal notch and the upper edge of the pubic bone (jugulum – symphysis distance, [Jug-Sy]) - which shows the strongest correlation to the true aortic length [88] and having the RT, the velocity of $PWV_{ao}$ can be calculated. The brachial augmentation index ($Aix_{brach}$) is calculated with the use of the formula: $(P2−P1/PP)*100$, where PP is the pulse pressure. The augmentation index of the aorta ($Aix_{ao}$) is calculated with the help of the invasively measured, very strong (R=0.94) linear correlation between $Aix_{brach}$ and $Aix_{ao}$ [86]. $SBP_{ao}$ is calculated as diastolic blood pressure (DBP) plus aortic/central pulse pressure ($PP_{ao}$). Measurements were taken at rest, after lying for 2–3 minutes in comfortable, supine position.

The use of Arteriograph is like oscillometric blood pressure measurement, which takes approximately 2 minutes and it is user-independent as it is fully automatic. Measured parameters are the following: peripheral or brachial blood pressure (SBP, DBP, MAP, PP, HR); central blood pressure ($SBP_{ao}$, $PP_{ao}$); augmentation index (Aix aortic, Aix brachial); aortic pulse wave velocity ($PWV_{ao}$); return time of aortic pulse wave ($RT_{ao}$); left ventricle ejection duration (ED); systolic area index (SAI); diastolic area index (DAI); diastolic reflection area (DRA); ankle – brachial index (ABI). Horváth and his co-workers [86] have registered arterial pressure waves in an adult patient invasively, while the cuff of the Arteriograph was placed on the upper arm (Figure 14). The edge of a high-fidelity pressure catheter was positioned in the brachial artery, just near the upper edge of the cuff (catheter was coming from the femoral artery, left subclavian artery, brachial artery). Using suprasystolic pressure cuff (+35 mmHg, brachial artery is occluded, there is no flow in the
artery; I. and II. pressure wave) two, separated systolic pressure peaks (red arrows, P₁, P₂) could be detected. By lowering the pressure in the cuff (around systolic blood pressure; III. pressure wave) the brachial artery opens, there is flow in the artery, but it is applanated. In this state, less distinguished systolic pressure peaks (black arrows, P₁, P₂) can be detected. Finally, lowering the pressure in the cuff (diastolic pressure, opened brachial artery; IV. and V. pressure wave) separated systolic peaks cannot be detected. Arteriograph requires I. and II. waveform for measurement, applanation tonometry uses waveform III., and devices (e.g., plethysmography) were design for non-invasive assessment of arterial function using this type of waveform (IV. V.) are not for arterial function measurement, but more for calculations of these parameters.

![Figure 14 Pulse pressure waves registered invasively in adult patient. By courtesy Horváth, Cziráki, Illyés.](image)

**Statistics**

To ensure data comparison between sexes, chi-squared test was carried out. Fisher’s exact test was applied to compare the prevalence with the previous Hungarian data. Data are reported as mean and SD for continuous data. For data comparison, Student’s t-test was carried out after checking that the assumption of normality was met. For statistical tests ‘p’ value <0.05 was used for significance. Multivariate linear regression cannot be applied due to the high multicollinearity among age, anthropometric and hemodynamic parameters in order to study causal relationships between OW/O and AFPs. Statistical analysis was performed with the SPSS 23.0 statistical package (SPSS Inc., Chicago, Illinois, USA).
Results

**Prevalence of overweight and obesity**

Table 3 contains the results of the prevalence of overweight and obesity. Out of the 6,824 subjects assessed, 2,881 boys (78.4% of the boys) and 2,580 girls (81.9% of the girls) had normal BMI. Altogether 14.1% of the boys (n=518) and 12.6% of the girls (n=397) were found to be overweight, while 7.5% of the boys (n=274) and 5.5% of the girls (n=174) were obese. In the total population studied, the prevalence of overweight was 13.4% (n=915), and 6.6% of obesity, which is 20% (n=1,363) of the studied population aged 3–18, in total.

Table 3 Prevalence of overweight and obesity in boys and girls

<table>
<thead>
<tr>
<th></th>
<th>Boys</th>
<th></th>
<th>Girls</th>
<th></th>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>normal BMI</td>
<td>2881</td>
<td>78.4</td>
<td>2580</td>
<td>81.9</td>
<td>5461</td>
<td>80</td>
</tr>
<tr>
<td>overweight</td>
<td>518</td>
<td>14.1</td>
<td>397</td>
<td>12.6</td>
<td>915</td>
<td>13.4</td>
</tr>
<tr>
<td>obese</td>
<td>274</td>
<td>7.5</td>
<td>174</td>
<td>5.5</td>
<td>448</td>
<td>6.6</td>
</tr>
<tr>
<td>overweight + obese</td>
<td>792</td>
<td>21.6</td>
<td>571</td>
<td>18.1</td>
<td>1,363</td>
<td>20</td>
</tr>
</tbody>
</table>

BMI; body mass index

Table 3 demonstrates that the rate of overweight and obesity is higher in the case of boys, than in the case of girls, since the total prevalence of overweight and obesity was 21.6% (n=792) in boys and 18.1% (n=571) in girls, this difference was proven by statistical analysis (chi-square test, p<0.005). Although absolute numbers are remarkable hallmarks of this study, the age and weight distribution of the participants is indicated in percentage, in order to ensure more informative data (Figures 15 and 16).
The total prevalence of overweight and obesity increases between the ages of 3 to 10 in both sexes, however, this increase is not even. The peaks are observed at the age of 10 in both
sexes. After puberty, there is a moderate decreasing trend both in boys and girls; however, the
decrease is more significant in girls.

Figure 17 represents our findings compared with the data previously measured in IDEFICS
and in the study of Antal and her co-workers in Hungary [89,90]. To ensure the comparability
of the data, our data have been determined in accordance with the age groups applied in the
previous studies (3–9 years, 7–14 years). Since prevalence is available only in percentages in
the HELENA and ENERGY studies and absolute numbers regarding Hungary are not
published therein, the proper statistical analysis in these cases could not be applied.
Statistically, compared to the previous Hungarian data, there has been no changes in any of
the sexes, in any respect (Fisher’s exact test, overweight p=0.055 and obesity p=0.66) in the
youngest age group (3–9 years). However, a slight decrease is observed in the prevalence,
since the p-value of the overweight is really close to the level of significance. In contrast, a
significant decrease is presented in the older age group (7–14 years), in both sexes, with
respect to overweight: the total prevalence has decreased from 20% to 15.3% (p<0.005),
while in this age group the prevalence of normal BMI increased from 72.7% to 76.4%
(p<0.001), and no difference is presented in the case of obesity (p=0.2). Prevalence of OW/O
in the studied population is detailed in Table 2. Among boys 518 were OW (14.1%), 274 were
O (7.5%), while in girls 397 (12.6%) were OW and 174 (5.5%) were O. The total prevalence
of OW and O was 21.6% in boys, while 18.1% in girls. Altogether 20% (n=1.363) of the
population were OW/O and 80% (n=5.461) of the participants were normal weighted. The
frequency of OW/O was significantly higher in boys (21.6%) than in girls (18.1%) (p≤0.001).
Comparison of normal weight, overweight and obesity prevalence between European data, latest Hungarian data and results from this study.*:[89]; **:[90].

**Arterial function parameters**

After excluding OW/O patients with momentary increased systolic and/or diastolic blood pressure regarding the relevant guideline, data from 326 OW and 105 O boys, and data from 243 OW and 45 O girls were analysed (Table 4).

The mean age of O boys (11.7±3.5 years) and O girls (11.5±3.7 years) were lower than of OW boys (12.4±3.9 years) and OW girls (12.6±3.8 years); however, the difference was not significant. No significant differences were detected regarding body height between OW/O patients and controls. According to the study design, the mean SBP<sub>brach</sub> values were equivalent in OW/O patients and controls. The mean diastolic blood pressure (DBP<sub>brach</sub>) values were slightly lower in every OW/O patient groups, and the difference was significant in O boys (p<0.003). Although heart rate (HR) was decreased in OW/O patients, the difference was not statistically proven.
Table 4 Characteristics of overweight and obese patients with normal systolic/diastolic blood pressure and controls

<table>
<thead>
<tr>
<th></th>
<th>control&lt;sub&gt;ow&lt;/sub&gt;</th>
<th>overweight</th>
<th>t-test</th>
<th>control&lt;sub&gt;ob&lt;/sub&gt;</th>
<th>obese</th>
<th>t-test</th>
<th>control&lt;sub&gt;ow&lt;/sub&gt;</th>
<th>overweight</th>
<th>t-test</th>
<th>control&lt;sub&gt;ob&lt;/sub&gt;</th>
<th>obese</th>
<th>t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>326</td>
<td>326</td>
<td>-</td>
<td>105</td>
<td>105</td>
<td>-</td>
<td>243</td>
<td>243</td>
<td>-</td>
<td>45</td>
<td>45</td>
<td>-</td>
</tr>
<tr>
<td>age (years)</td>
<td>12.4 ± 3.9</td>
<td>12.4 ± 3.9</td>
<td>0.9910</td>
<td>NS</td>
<td>11.7 ± 3.5</td>
<td>11.7 ± 3.5</td>
<td>0.9882</td>
<td>NS</td>
<td>12.6 ± 3.8</td>
<td>0.9946</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>height (cm)</td>
<td>155.5 ± 22.5</td>
<td>156.4 ± 21.7</td>
<td>0.5999</td>
<td>NS</td>
<td>151.2 ± 20.2</td>
<td>155.3 ± 19.3</td>
<td>0.1301</td>
<td>NS</td>
<td>152.3 ± 18.8</td>
<td>0.6693</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>weight (kg)</td>
<td>46.0 ± 17.4</td>
<td>59.1 ± 20.6</td>
<td>0.0000</td>
<td>p &lt; 0.00001</td>
<td>41.9 ± 15.4</td>
<td>69.4 ± 24.0</td>
<td>0.0000</td>
<td>p &lt; 0.00001</td>
<td>44.0 ± 14.9</td>
<td>0.0000</td>
<td>p &lt; 0.00001</td>
<td></td>
</tr>
<tr>
<td>BMI (%)</td>
<td>18.1 ± 2.8</td>
<td>23.1 ± 2.9</td>
<td>0.0000</td>
<td>p &lt; 0.00001</td>
<td>17.6 ± 2.5</td>
<td>27.6 ± 4.3</td>
<td>0.0000</td>
<td>p &lt; 0.00001</td>
<td>18.2 ± 2.8</td>
<td>0.0000</td>
<td>p &lt; 0.00001</td>
<td></td>
</tr>
<tr>
<td>SBP&lt;sub&gt;brach&lt;/sub&gt; (mmHg)</td>
<td>118.8 ± 9.6</td>
<td>118.9 ± 9.6</td>
<td>0.9416</td>
<td>NS</td>
<td>117.4 ± 9.1</td>
<td>117.8 ± 9.2</td>
<td>0.7235</td>
<td>NS</td>
<td>116.6 ± 7.8</td>
<td>0.9481</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>DBP&lt;sub&gt;brach&lt;/sub&gt; (mmHg)</td>
<td>66.5 ± 6.0</td>
<td>66.5 ± 6.4</td>
<td>0.8653</td>
<td>NS</td>
<td>67.9 ± 6.0</td>
<td>65.3 ± 5.8</td>
<td>0.0021</td>
<td>p &lt; 0.003</td>
<td>67.2 ± 6.0</td>
<td>0.4369</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>84.0 ± 6.3</td>
<td>84.0 ± 6.7</td>
<td>0.9472</td>
<td>NS</td>
<td>84.3 ± 6.2</td>
<td>82.8 ± 5.9</td>
<td>0.0755</td>
<td>NS</td>
<td>83.8 ± 6.1</td>
<td>0.4890</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>HR (1/min)</td>
<td>76.9 ± 13.8</td>
<td>75.9 ± 13.2</td>
<td>0.3534</td>
<td>NS</td>
<td>79.1 ± 14.8</td>
<td>76.1 ± 11.4</td>
<td>0.1051</td>
<td>NS</td>
<td>80.5 ± 12.7</td>
<td>0.1081</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>PWV&lt;sub&gt;ao&lt;/sub&gt; (m/s)</td>
<td>5.8 ± 0.8</td>
<td>5.8 ± 0.8</td>
<td>0.5383</td>
<td>NS</td>
<td>5.7 ± 0.6</td>
<td>5.8 ± 0.7</td>
<td>0.5980</td>
<td>NS</td>
<td>5.8 ± 0.7</td>
<td>0.0486</td>
<td>p &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>Aix&lt;sub&gt;ao&lt;/sub&gt; (%)</td>
<td>7.8 ± 7.2</td>
<td>7.2 ± 6.9</td>
<td>0.2802</td>
<td>NS</td>
<td>9.5 ± 8.7</td>
<td>6.7 ± 7.0</td>
<td>0.0119</td>
<td>p &lt; 0.02</td>
<td>10.2 ± 6.8</td>
<td>0.0035</td>
<td>p &lt; 0.004</td>
<td></td>
</tr>
<tr>
<td>SBP&lt;sub&gt;ao&lt;/sub&gt; (mmHg)</td>
<td>104.8 ± 7.7</td>
<td>104.3 ± 7.9</td>
<td>0.4419</td>
<td>NS</td>
<td>104.6 ± 7.5</td>
<td>103.2 ± 7.3</td>
<td>0.1817</td>
<td>NS</td>
<td>103.9 ± 6.9</td>
<td>0.4112</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

BMI; body mass index, SBP<sub>brach</sub>; systolic brachial blood pressure, DBP<sub>brach</sub>; diastolic brachial blood pressure, MAP; mean arterial blood pressure, HR; heart rate, PWV<sub>ao</sub>; aortic pulse wave velocity, Aix<sub>ao</sub>; aortic augmentation index, SBP<sub>ao</sub>; aortic systolic blood pressure, NS; not significant, control<sub>ow</sub>; overweight control group, control<sub>ob</sub>; obese control group.
PWV\textsubscript{ao} did not show significant differences either in OW, or in O boys, or in O girls compared to controls (5.8±0.8 m/s OW boys vs 5.8±0.8 m/s controls, 5.7±0.6 m/s O boys vs 5.8±0.7 m/s controls, 5.7±0.8 m/s O girls vs 5.8±0.7 m/s controls), while it was significantly lower in OW girls than in controls (5.8±0.7 m/s OW girls vs 5.6±0.8 m/s controls, p<0.05) (Figure 18 and 19).

![Figure 18](image18.png)

**Figure 18** PWV\textsubscript{ao} values in OW and O subjects and controls, boys. NS; non-significant.

![Figure 19](image19.png)

**Figure 19** PWV\textsubscript{ao} values in OW and O subjects and controls, girls. NS; non-significant, *, p<0.05

Aix\textsubscript{ao} was lower in every OW/O patients groups. The differences were significant in O boys (6.7±7.0% O boys vs 9.5±8.7% controls, p<0.02) and in OW girls (8.4±6.6% OW girls vs 10.2±6.8% controls, p<0.004), while it did not differ statistically either in OW boys
(7.2±6.9% vs 7.8±7.2% in controls, NS) or in O girls (8.5±5.8% in O girls vs 10.8±9.1% in controls, NS) (Figure 20 and 21).

**Figure 20** Aix\textsubscript{ao} in OW and O subjects and healthy controls, in boys. NS; non-significant. *; p<0.02

**Figure 21** Aix\textsubscript{ao} in OW and O subjects and healthy controls, in girls. NS; non-significant, *; p<0.004
SBP<sub>ao</sub> did not differ significantly either in boys, or in girls, nevertheless, SBP<sub>ao</sub> was slightly lower in O/OW patients (104.3±7.9 mmHg in OW boys vs 104.8±7.7 mmHg in controls, 103.2±7.3 mmHg in O boys vs 104.6±7.5 mmHg in controls, while 103.4±7.1 mmHg in OW girls vs 103.9±6.9 mmHg in controls, 102.4±6.9 mmHg in O girls vs 103.5±6.6 mmHg in controls) (Figure 22 and 23).

**Figure 22** SBP<sub>ao</sub> in OW and O subjects and healthy controls, in girls. NS; non-significant.

**Figure 23** SBP<sub>ao</sub> in OW and O subjects and healthy controls, in girls. NS; non-significant.
Discussion

**Prevalence of overweight and obesity**

The prevalence of overweight and obesity is constantly increasing in children, adolescents, and adults, in developed and developing countries, as well [4]. This condition – beside several other profound consequences – raises the risk of cardiovascular mortality, thus on the one part substantially shortens life expectancy for persons, and on the other part, imposes a burden on health care and social welfare systems. Figure 24 represents the increment of mean BMI worldwide and in Hungary between 1975 and 2016 in children aged between 5 and 19 years. The global mean BMI raised from 16.8 kg/m² to 18.5 kg/m² in boys, whereas in girls mean BMI reveals the same increment: from 17.2 kg/m² to 18.6 kg/m². The Hungarian mean BMI increased from 18.8 kg/m² to 20.0 kg/m² in boys, and from 18.2 kg/m² to 19.9 kg/m² in girls.

![Mean BMI in the World and Hungary between 1975 and 2016 in boys and girls aged between 5 and 19 years](image)

In the ranking of 200 countries -where 1st place means the most overweight or obese country-, regarding mean BMI in boys, Hungary moved to the 65th place (2016) from the 23rd (1975), and from 79th (1975) to 70th (2016) place in girls. In the same ranking, but regarding overweight, Hungarian boys are at the 50th place (from the 46th place) and girls stepped “forward” to the 99th place from 78th place. In the case of obesity, Hungarian boys are on the 51st place (from 54th) and girls became 85th from 64th. According to these results, the mean BMI for girls and the prevalence of obesity did not show any improvement in the position out of the 200 involved countries. Nauru, Cook Islands and Paulu are in the top three in the rank of overweight and obesity, meanwhile Vietnam, Cambodia, India, Burkina Faso and Nepal are represented in the last 5 positions on these lists [4]. Figure 25 shows alterations of the
mean BMI in the World compared to Hungary. It is clearly visible, that in 1975 the global mean BMI was lower than in Hungarian boys and girls. In 2016, the mean BMI in the World was 18.5 kg/m² in girls and 18.6 kg/m² in boys, while the mean BMI in Hungarian girls was 19.9 kg/m² and 20.0 kg/m² in boys.

Figure 25 Distribution of mean BMI in the World, in boys and girls, 1975-2016. Black arrow: world mean, red arrow: mean BMI in Hungary [4].
Studies have suggested that there is a strong correlation between elevated BMI and geographical location, local habits and traditions, socio-economic culture, considering eating habits as well as physical activity patterns [91,92]. Changes in environmental factors, lifestyle, eating habits and in physical activity may affect the prevalence of overweight and obesity in a negative or positive way, as well. Such changes and the geo-economical differences justify the repeat of large population studies, in order to follow-up potential changes in the frequency of overweight and obesity. For this purpose, several studies have been carried out in Europe involving more than 10 European countries, including Hungary. In the “HELENA” study [93] adolescents (aged 12.5−17.5 years) between 2002 and 2006, in the “IDEFICS” [89] study children (aged 2−9 years) between 2006 and 2012, and the “ENERGY” study [94] children aged 10−12 years between 2010 and 2013 were assessed. These three projects cover a remarkable period of time (>11 years). Antal and her co-workers have conducted their study in the first semester of the academic year 2005/2006 [57]. Our research lasted for 4 years, and the 3−18-year-old population was basically assessed simultaneously. Due to such circumstances, our findings may give a more accurate picture of the condition of a well-balanced, young generation with significant number (n=6.824) of participants. In our study, the prevalence of overweight and obesity was significantly higher in boys than in girls. Our findings essentially correspond to the global prevalence published by Ng and her co-workers [3]. According to our results, prevalence of overweight and obesity was significantly higher in boys than in girls. BMI differences between the sexes have long been recognized [95]. Such differences may arise from biological, sociological and cultural differences, or perhaps from the combined effect of these [96,97]. There is a close correlation between the total energy expenditure (TEE) and body weight [98]. Goran and his co-workers found in their longitudinal study, that between the age of 5 to 10 years TEE is continuously increasing in the case of boys, however in the case of girls, this marker rises from 1.400 kcal (at age 5) to 1.800 kcal (at age 6) and falls to 1,600 kcal (at age 9). This significant decrease is due to the fact that the girls’ physical activity decreases by 50% between the age 6 to 9 years [99]. Studies have found that adolescent girls are more likely to give attention to healthy nutrition, whilst boys are more apt to consume more fast food. These differences may stem from the Western societies’ perception of the ideal body figure and from the fact that certain foods are gendered. For example, power and virility is symbolized by meat, therefore men eat
more meat than women, while fat and carbohydrate rich foods are more often consumed by women in accordance with their menstrual cycle [100].

The above described reasons may explain the age-related increase in prevalence of overweight and obesity, namely that it increases between the age of 3 and 10 in both sexes, and afterwards shows a gradual decrease in both sexes; however, such decrease is more significant in the case of girls.

One of the most important observation of this study is that compared to the previous Hungarian data, mild decrease occurred in the youngest age group (3–9 years) in both sexes, in respect of overweight. Furthermore, the prevalence of overweight significantly decreased, while the prevalence of normal BMI significantly increased in the older age group (7–14 years).

The fact that the total prevalence of overweight and obesity has not significantly changed in the age group 3–9 year compared to the previous Hungarian researches, may be explained by several factors. The lower supply of protein from human milk (9 and 10 g/d at ages 3 and 6 month) as compared with formula (14 and 18 g/d, respectively) [101] might attenuate both early weight gain and later obesity [102]. One of the best predictors of later obesity risk is weight gain during the first year of life [103–105]. Recent studies have pointed out that increased protein intake (+6–8 g daily) during the first year of life could lead to 2.43 times higher risk for obesity at the age of 6 [106]. Moreover, the daily rhythm of nutrition of this age group is not well-balanced, some meals are often omitted, which may also increase the risk of obesity [107]. Since parents have the greatest influence on nutrition at this age, they may have a key role at eliminating these anomalies. Consequently, education of parents in the field of nutrition is crucial, since they are the ones who are mostly responsible for the daily eating routine of their children.

Recognising these factors, several acts have been adopted in Hungary aimed to prevent obesity in childhood (daily physical education, regulation of the products offered at the school buffet, maximized trans-fatty acids in products).

When examining the prevalence of these conditions in other European countries we have found that in Switzerland the total prevalence of overweight and obesity shows a significant decline, due to the school-based promotion of physical activity and healthy nutrition. In France and Sweden data demonstrate that the raising trend has stopped, similarly to the United Kingdom, where it has reached its peak in 2005 (26.4%) and no notable change was observed until 2008 [108].
Detailed interview questionnaire (physical activity patterns and nutritional habits) is required to assess the examined progress, and the measurement of hip, waist circumference, and upper arm skinfold thickness are planned in the future. These arrangements might provide more informative results, supporting to understand the possible underlying causes of the prevalence of increased BMI. Nearly two-third of the Hungarian adults (65% in men, 60% in women) are overweight or obese based on their BMI [109]. Such abnormal condition is rooted in childhood and adolescence. Results from this study suggest that overweight and obesity is present in 20% of the 3–18-year-old population. This fact draws attention to the importance of prevention, healthy nutrition and regular physical activity.

**Arterial function parameters**

*Arterial function parameters in overweight and obese children and adolescents—overview of the relevant literature*

Alterations of AFPs might be detected in overweight or obese children and adolescents. Numerous papers (cc. 400) were published concerning this issue; however, only a few high-quality studies are available, which detail the AFPs in this population. After a rigorous review of literature, we analysed the data of eight papers [110–117] (a total of 378 O and 85 OW patients) (Table 5). In these studies, small groups of O/OW patients (n<104) were included; moreover, the age-range of the studied OW/O patients as narrow (average 10.2—14.2 years).

The authors used ultrasound and applanation tonometry to determine $\text{PWV}_{\text{ao}}$, which are limited in use in the non-invasive clinical evaluation of aortic stiffness in pediatric patients [42]. $\text{Aix}_{\text{ao}}$ data were published only in three papers (total of 38 O, 85 OW patients) [111,115,116], while $\text{SBP}_{\text{ao}}$ was measured merely in three studies (total of 122 O patients), as well [111,116,117].

These researchers have pointed out that the $\text{PWV}_{\text{ao}}$ was higher in O patients compared to control subjects. Only Mocnik and her co-workers have detected no difference in $\text{PWV}_{\text{ao}}$ values; nevertheless, they measured OW and not O patients [115]. Aortic stiffness is strongly influenced by the actual systolic blood pressure (SBP) [42]. Moreover, $\text{PWV}_{\text{ao}}$ rises with increasing age especially after the beginning of puberty in both sexes [70]. Consequently, if we would like to compare this parameter, SBP and age should be identical in patients and controls. Hemodynamics is a complex, dynamically changing system in which alteration of one parameter causes fluctuation in others. To explore the possible
pathophysiology of hemodynamics in O/OW patients AFPs and peripheral/brachial SBP (SBP\textsubscript{brach}) should be measured at the same time. Reviewing the cited eight studies (Table 5), only two papers fulfil the aforementioned criteria regarding age [111,116], but none of them execute the assumption of simultaneous measurements of AFPs and SBP\textsubscript{brach}. 
Table 5 Summary of included studies, individual study details, and findings of arterial function assessment

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Number of patients</th>
<th>Sex ratio</th>
<th>Obesity definition</th>
<th>Method of PWV measurement</th>
<th>SBP&lt;sub&gt;brach&lt;/sub&gt; (mmHg)</th>
<th>DBP&lt;sub&gt;brach&lt;/sub&gt; (mmHg)</th>
<th>PWV&lt;sub&gt;ao&lt;/sub&gt; (m/s)</th>
<th>Aix&lt;sub&gt;ao&lt;/sub&gt; (%)</th>
<th>SBP&lt;sub&gt;ao&lt;/sub&gt; (mmHg)</th>
<th>Author / year of publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.2 ± 2.0</td>
<td>30 obese</td>
<td>40% male</td>
<td>BMI&gt;95</td>
<td>Echo Doppler</td>
<td>110 (100-110)</td>
<td>70 (65-70)</td>
<td>4.0 ± 0.8</td>
<td>no</td>
<td>no</td>
<td>Celik, 2011 [110]</td>
</tr>
<tr>
<td>12.5 ± 1.7</td>
<td>30 non-obese</td>
<td>43% male</td>
<td></td>
<td></td>
<td>90 (90-95)</td>
<td>60 (60-65)</td>
<td>3.3 ± 0.7</td>
<td>no</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>13.8 ± 2.3</td>
<td>61 obese</td>
<td>56% male</td>
<td>BMI&gt;95</td>
<td>Echo Doppler</td>
<td>114 ± 13</td>
<td>62 ± 9</td>
<td>4.9 ± 1.4</td>
<td>no</td>
<td>no</td>
<td>Harris, 2012 [112]</td>
</tr>
<tr>
<td>13.8 ± 4.0</td>
<td>55 non-obese</td>
<td>40% male</td>
<td></td>
<td></td>
<td>107 ± 11</td>
<td>64 ± 8</td>
<td>3.5 ± 0.5</td>
<td>no</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>14.2 ± 2.0</td>
<td>21 obese</td>
<td>81% male</td>
<td>BMI&gt;95</td>
<td>applanation tonometry</td>
<td>117 ± 14</td>
<td>57 ± 6</td>
<td>5.9 ± 1.1</td>
<td>-1 ± 12</td>
<td>96 ± 12</td>
<td>Koopman, 2012 [111]</td>
</tr>
<tr>
<td>13.9 ± 2.3</td>
<td>27 non-obese</td>
<td>81% male</td>
<td></td>
<td>SphygmoCor</td>
<td>108.8 ± 8</td>
<td>54 ± 6</td>
<td>4.7 ± 1</td>
<td>-11 ± 13</td>
<td>86 ± 7</td>
<td></td>
</tr>
<tr>
<td>13.2 ± 1.8</td>
<td>61 obese</td>
<td>49% male</td>
<td>BMI&gt;95</td>
<td>applanation tonometry</td>
<td>115 (90-160)</td>
<td>75 (50-117)</td>
<td>5.0 ± 0.7</td>
<td>no</td>
<td>no</td>
<td>Hacihamdioglu, 2014 [113]</td>
</tr>
<tr>
<td>13.2 ± 2.1</td>
<td>58 non-obese</td>
<td>48% male</td>
<td></td>
<td>SphygmoCor</td>
<td>106.6 ± 6.5</td>
<td>64.7 ± 5.7</td>
<td>4.7 ± 0.5</td>
<td>no</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>12.6 (11.4-15)</td>
<td>104 obese</td>
<td>48% male</td>
<td>Danish standard</td>
<td>applanation tonometry</td>
<td>110.9 ± 8.5</td>
<td>61.8 ± 5.7</td>
<td>4.5 ± 0.5</td>
<td>no</td>
<td>no</td>
<td>Hvidt, 2015 [114]</td>
</tr>
<tr>
<td>13.2 (11.7-14.9)</td>
<td>50 non-obese</td>
<td>46% male</td>
<td>SphygmoCor</td>
<td>107.7 ± 8.0</td>
<td>59.1 ± 5.3</td>
<td>4.3 ± 0.5</td>
<td>no</td>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.7 ± 3.8</td>
<td>85 overweight</td>
<td>51% male</td>
<td>BMI≥90</td>
<td>applanation tonometry</td>
<td>129.5 ± 16.6</td>
<td>76.3 ± 10.7</td>
<td>6.1 ± 6.3</td>
<td>-18 ± 15.5</td>
<td>no</td>
<td>Mocnik, 2015 [115]</td>
</tr>
<tr>
<td>12.7 ± 3.4</td>
<td>50 non-obese</td>
<td>30% male</td>
<td></td>
<td>SphygmoCor</td>
<td>115.6 ± 11.7</td>
<td>67.7 ± 7.9</td>
<td>6.1 ± 1.2</td>
<td>-14.8 ± 14.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.6 ± 2.7</td>
<td>84 obese</td>
<td>51% male</td>
<td>BMI&gt;2</td>
<td>applanation tonometry</td>
<td>113 ± 11</td>
<td>60 ± 7</td>
<td>4.8 ± 1.4</td>
<td>no</td>
<td>94 ± 10</td>
<td>Garcia-Espinosa, 2016 [117]</td>
</tr>
<tr>
<td>10.9 ± 2.8</td>
<td>137 non-obese</td>
<td>72% male</td>
<td></td>
<td>SphygmoCor</td>
<td>108 ± 11</td>
<td>60 ± 8</td>
<td>4.7 ± 0.7</td>
<td>no</td>
<td>91 ± 9</td>
<td></td>
</tr>
<tr>
<td>10.2 ± 3</td>
<td>17 obese</td>
<td>47% male</td>
<td>BMI&gt;2</td>
<td>applanation tonometry</td>
<td>112 ± 11</td>
<td>59±8</td>
<td>4.6 ± 0.7</td>
<td>0.9 ± 10.5</td>
<td>95 ± 10</td>
<td>Castro, 2016 [116]</td>
</tr>
<tr>
<td>9.9 ± 3.2</td>
<td>26 non-obese</td>
<td>52% male</td>
<td></td>
<td>SphygmoCor</td>
<td>106 ± 12</td>
<td>60±8</td>
<td>4.5 ± 0.7</td>
<td>6.5 ± 9.7</td>
<td>90 ± 11</td>
<td></td>
</tr>
</tbody>
</table>

PWV; pulse wave velocity, SBP<sub>brach</sub>; systolic brachial blood pressure, DBP<sub>brach</sub>; diastolic brachial blood pressure, PWV<sub>ao</sub>; aortic pulse wave velocity, Aix<sub>ao</sub>; aortic augmentation index, SBP<sub>ao</sub>; aortic systolic blood pressure, BMI; body mass index
In this study, simultaneously measured AFPs and SBP\textsubscript{brach} have been registered in OW/O patients and healthy controls, and these groups were accurately matched for age, height and SBP\textsubscript{brach}.

The most important findings of this study regarding AFPs are the following: Firstly, PWV\textsubscript{ao} was not higher in OW/O patients. Secondly, Aix\textsubscript{ao} was lower in OW/O patients. Thirdly, SBP\textsubscript{ao} did not differ significantly measured in OW/O patients and controls. Fourthly, the effects of OW and O on AFPs were practically the same.

Our study provides remarkable number of AFPs data of OW/O patients in the relevant literature, owing to a new, occlusive-oscillometric, “one-cuff” method, which brought a new era in the field of AFPs measurement, especially in children. Recently, reference values of PWV\textsubscript{ao} [70,118], Aix\textsubscript{ao} [76,77] and SBP\textsubscript{ao} [83] for children and adolescents have been published, which proves that AFPs vary physiologically with the increasing age during childhood and adolescence.

Reviewing the methods used for AFPs measurements in the previously published papers cited (Table 4); Doppler ECHO and applanation tonometry were applied. By using Doppler ECHO, only PWV\textsubscript{ao} can be measured [78]; this method is not appropriate for measuring Aix\textsubscript{ao} and SBP\textsubscript{ao}. Although applanation tonometry measures AFPs, it does not measure the SBP\textsubscript{brach} simultaneously; so far, the SBP\textsubscript{brach} has been measured at the beginning of the measuring procedure, and AFPs are calculated later by the device.

**PWV\textsubscript{ao}**

Analysing the reference values of PWV\textsubscript{ao} measured in children and adolescents [70], it is apparent that the median curve shows a flat period between the age of three and the beginning of puberty with a steeper increase thereafter in both sexes. Therefore, it is crucial to match for age of the investigated patients and control groups precisely. Only three publications were found [112,113,115] in which the mean age of the examined groups was identical.

Moreover, PWV\textsubscript{ao} is dependent on the SBP\textsubscript{ao} [42]. SBP\textsubscript{ao} has been measured in three studies and the authors have found that it was increased in the OW/O groups compared to the controls [46,47,49]. In these investigations, elevated PWV\textsubscript{ao} may originate from older age, increased SBP\textsubscript{ao}, from OW/O or from the combined effect of all these. Eliminating these possible modifying factors, age and SBP\textsubscript{brach} matched control groups were formed in our study. Because of this, no significant differences were found regarding PWV\textsubscript{ao} either in OW/O boys, or in OW/O girls. Moreover, PWV\textsubscript{ao} was significantly lower in OW girls than in control cases.
It is known that fatty streaks may occur on the aortic wall even in the fetus due to maternal hypercholesterolemia [119]. Moreover, in the P-DAY study fibrous plaques on the abdominal aortic wall have been found in 13.8% of white boys and in 6.8% of white girls aged 15—19 years [36]. OW and O might cause disturbances in lipid metabolism [120]; consequently, accelerated, intensive formations of fatty streaks and fibrous plaques could not be excluded in OW and O children and adolescents.

Based on our findings, these presumed phenomena (fatty streaks; and fibrous plaques) might not influence the physical features of the aortic wall, and therefore aortic stiffness may remain unaltered in this age period in the OW/O population.

### $Aix_{ao}$

$Aix_{ao}$ data from OW/O children and adolescents published previously are conflicting. Koopman has found that $Aix_{ao}$ was higher in O patients [111], while Mocnik [115], and Castro [116] has measured lower $Aix_{ao}$ in OW/O patients than in controls. In our study the $Aix_{ao}$ was consonantly lower in OW/O patients groups, and the differences were significant in OW girls and O boys. The difference was remarkable in O girls, as well, but it has not been proven statistically due to the high standard deviation of mean values of control group.

This finding could be explained by the increased metabolism observed in OW/O patients [121], which causes a remarkable increase in stroke volume and heart rate, consequently the cardiac output elevates notably. Due to the increased cardiac output and the concomitantly increasing SBP, the lateral tension towards the aortic wall is also increased; thus, the aortic wall becomes stiffer and, as its consequence, the $PWV_{ao}$ will be higher. We may hypothesize, that to compensate the increased cardiac output and SBP, the vascular regulation system lowers the $TPVR$ by dilating the small arterioles; therefore, decreased $Aix_{ao}$ can be detected [122].

### $SBP_{ao}$

$SBP_{ao}$ has been measured and published previously in OW/O children and adolescents by three working groups [111,116,117], and increased $SBP_{ao}$ has been found by all of them compared those measured in controls. In these studies, $SBP_{brach}$ was higher in OW/O patients than in controls; therefore, we suppose that the increased $SBP_{ao}$ may be caused by elevated $SBP_{brach}$. In our study, no significant differences were found regarding $SBP_{ao}$ in OW/O patients and controls; however, $SBP_{ao}$ was slightly lower in OW/O patients. This finding can
be explained by our study design: SBP\textsubscript{brach} was precisely matched in OW/O patients and controls; hence, - based on the formerly discussed relationship between SBP\textsubscript{brach} and SBP\textsubscript{ao} – the SBP\textsubscript{ao} could not be higher than the SBP\textsubscript{brach}. The slight lowering of SBP\textsubscript{ao} detected in OW/O patients may be the consequence of the decreased Aix\textsubscript{ao}, otherwise the diminished TPVR.
Conclusions

Prevalence of overweight and obesity

Nearly two-third of the Hungarian adults (65% in men, 60% in women) are overweight or obese based on their BMI [109]. Such abnormal condition is rooted in childhood and adolescence. Our study comprises a considerable number of subjects. Results from this study suggest that overweight and obesity is present in 20% of the 3–18-year-old population. This fact draws attention to the importance of prevention, healthy nutrition and regular physical activity.

Arterial function parameters

Based on our results, we may conclude that the increased cardiac output and elevated sympathetic outflow due to childhood OW/O are compensated hemodynamically, resulting in the opening of the small arterioles, lowering the TPVR (Aix\textsubscript{ao} decreases), subsequently SBP\textsubscript{brach} and SBP\textsubscript{ao} remain normal.

Therefore, we suppose that OW/O might not have direct and irreversible effect on the arterial function in the investigated age group. Successful lifestyle intervention programs (focusing on weight reduction, cessation of sedentary lifestyle, sleeping, stress elimination, and relaxation) may lead to the optimization of the CV risks in the affected subjects.

Following these OW/O patients with regular non-invasive monitoring of AFPs combining with different tests, we may be able to detect the phase, where the haemodynamic compensation of the arterial functions switches into deterioration, resulting in unfavourable changes regarding AFPs. In the future, our working group will focus on this issue.
Summary

Conclusions of the studies presented in the thesis are:

1. We have found the prevalence of overweight and obesity in total is 20% in Szolnok and its surrounding area, namely 13.4% of the patients were overweight, 6.6% were obese.
2. Compared to the previous Hungarian data, we have identified a mild decrease in the youngest age group (3–9 years) in both sexes, in respect of overweight.
3. We have established, that the prevalence of overweight significantly decreased, while the prevalence of normal BMI significantly increased in the older age group (7–14 years).
4. Our study provides remarkable number of AFPs data in OW/O patients (n=719).
5. By creating proper control groups, no significant differences were found regarding PWV\textsubscript{ao} either in OW/O patients.
6. We may conclude, that lower Aix\textsubscript{ao} in OW/O patients, may stem from the decreased TPVR in order to compensate the increased metabolism presented in OW/O patients.
7. We could not identify significant differences regarding SBP\textsubscript{ao} in OW/O patients.
ACKNOWLEDGEMENTS

First of all, I would like to say thank you to Prof. Dr. Lajos Kemény, DSA the program director of Clinical Medical Sciences Doctoral School to enable me to study in this doctoral program.

I also would like to express my appreciation to my consultant, Dr. Csaba Bereczki, PhD who always supported and encouraged me during my PhD studies.

I am thankful to Zoltán Maróti PhD and Tibor Kalmár PhD for their constant help in every aspect of the writing of this thesis and my publications. I am very grateful for their guidance.

I would like to thank Dr. Miklós Illyés, PhD for teaching me the theoretical background of this device, the Arteriograph and Prof. Dr. Attila Cziráki, PhD for sharing his knowledge with me.

I am very grateful to Prof. Dr. István Raskó, DSA for giving me scientific advices, helping me to build the structure of my PhD and being an overall help during my studies.

I wish to thank Gábor Érsek for his help in the field of statistics and data analyzing and I also want to thank dr. Judit Kelemen and Csilla Keresztes, PhD for being the lecturer of my publications.

I am very thankful to my friends and family, especially to my mother who helped me all the way with her scientific experience, supported with her enthusiasm, I cannot express my appreciation enough for her investment in this thesis.
References

1. WHO | World Health Organization. WHO 2018;


44


83 Program D, Doktora MTA, Ph A: Az art ériás pulzushullám non - invazív oszillometriás vizsgálata gyermekekben és serdülőkben 2013;


94 van Stralen MM, te Velde SJ, Singh AS, De Bourdeaudhuij I, Martens MK, van der


I.
II.