Diploma Thesis

Prevalence of arterial hypertension in adolescents in underdeveloped regions of Mthatha, South Africa

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Graz, am 19.05.2020 *Michael Gaisl eh.*

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Abbreviations

BMI.....body mass index
CCBs.....calcium channel blockers
CVD.....cardiovascular disease
DBP.....diastolic blood pressure
ESC.....European Society of Cardiology
GHS.....General Household Survey
HMOD.....hypertension-mediated organ damage
MAP.....mean arterial pressure
OSA.....obstructive sleep apnoea
PH.....primary hypertension
RAAS..... renin-angiotensin aldosterone system
SPB.....systolic blood pressure
SPC.....single-pill combination
WHO.....World Health Organization

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Zusammenfassung

Hintergrund

Bluthochdruck und kardiovaskuläre Risikofaktoren im Allgemeinen, stellen seit einigen Jahren ein gesellschaftliches Gesundheitsproblem in Südafrika dar. Bluthochdruck ist einer der häufigsten Risikofaktoren für Herz-Kreislauf-Erkrankung. Die Daten zur Prävalenz von arteriellem Bluthochdruck von Jugendlichen in Südafrika deuten ebenfalls auf eine hohe Prävalenz hin. Daten, ob Jugendliche in unterentwickelten Gebieten Südafrikas ebenfalls betroffen sind, werden benötigt. Das Ziel dieser Diplomarbeit ist die Erfassung der Prävalenz arterieller Hypertonie und die Erforschung des Zusammenhangs mit Fettleibigkeit Jugendlichen in ländlichen Schulen rund um die Stadt Mthatha in Südafrika.

Material und Methoden

244 Jugendliche (188 Frauen, 56 Männer) im Alter von 13-16 Jahren wurden in die Studie eingeschlossen. Von allen Teilnehmern wurden Daten von Bluthochdruck, Größe und Gewicht ermittelt. Anschließend wurden BMI und Blutdruckwerte in Perzentilen aufgetragen, welche Geschlecht, Alter und Größe berücksichtigen, um zu ermitteln, ob der/die jeweilige Jugendliche Bluthochdruck hat oder übergewichtig ist.

Ergebnisse

Mehr als ein Drittel (38.9%) aller Studienprobanden hatten erhöhte Blutdruckwerte. 16% aller Teilnehmer waren übergewichtig und 15.6% hatten Adipositas Grad I bis III. Bei Übergewichtigen/Adipösen Jugendlichen lag die Prävalenz von Bluthochdruck sogar bei 61.0% (47/77), jedoch war diese mit 28.7% (48/167) auch bei schlanken Jugendlichen relativ hoch. Die Häufigkeit von Bluthochdruck in Übergewichtigen/Adipösen Personen war damit signifikant höher als in schlanken Jugendlichen. Mittlerer systolischer Blutdruck korrelierte dabei stärker mit BMI als mit mittlerem diastolischem Blutdruck. Das Geschlecht der Jugendlichen hatte dabei keinen signifikanten Einfluss auf die Häufigkeit von Bluthochdruck.

Conclusio

Bluthochdruck und Adipositas haben unabhängig voneinander und zusammen eine hohe Prävalenz in jugendlichen Schülern aus Mthatha. Dadurch hat annähernd die Hälfte aller Studienprobanden ein stark erhöhtes Risiko in ihrem Leben an einer Herz-Kreislauf-Erkrankung zu erkranken. Die Ergebnisse bestärken die Notwendigkeit einer effektiven Früherkennung von Bluthochdruck in Jugendlichen. Strategien für Präventions- und Aufklärungsmaßnahmen, um weitere Gefäßschäden in SchülerInnen für die Zukunft zu vermeiden, sollten implementiert werden. Weitere Longitudinalstudien sind notwendig, um herauszufinden, wie sich die gefundenen kardiovaskulären Risikofaktoren im Erwachsenenalter auswirken.

Abstract

Background

One of the biggest known risk factors for cardiovascular diseases (CVDs) is hypertension. Hypertension and other risk factors for CVDs are a rising public health problem for South Africa. Prevalence of hypertension seems to be alarmingly high. The aim of this study is to assess the prevalence of hypertension and examine the correlation with overweight and obesity in school-attending adolescents of Mthatha, South Africa.

Methods

In a cross-sectional study two hundred and forty-four (188 females, 56 males) aged 13 – 16 years were recruited. Blood pressure, height and weight were assessed from all individuals. Subsequently, blood pressure percentiles adjusted for gender, age, and height, and body mass index (BMI) were calculated to determine presence of hypertension and obesity, respectively.

Results

The overall prevalence of pre-hypertension and hypertension was over a third (38.9%) and almost one third (31.6%) of adolescents were either overweight or obese. Prevalence of pre-hypertension and hypertension in overweight and obese individuals was at 61.0% (47/77) but also in lean adolescents a fairly high prevalence of 28.7% (48/167) was found to be present. Therefore, prevalence of hypertension was found to be significantly higher in overweight/obese adolescents compared to lean individuals. Systolic blood pressure (SBP) had a stronger correlation with BMI than diastolic blood pressure (DBP). Gender was not a significant risk factor for development of hypertension.

Conclusions

Pre-hypertension/hypertension and overweight/obesity, combined and independently, have a high prevalence in South African students. Therefore, almost half of adolescents included in this study are at risk for CVDs. Results confirm the need for preventive screening for hypertension in adolescents. To prevent a high incidence of CVDs, intervention strategies are needed. Further longitudinal studies are required to determine the impact of these cardiovascular risk factors into adulthood.

1 Introduction

Arterial hypertension poses a significant and rising medical burden in recent years. Estimates of the World Health Organization (WHO) about the prevalence of hypertension in 2005 were already too low and the current prevalence of hypertension worldwide should have been reached only as late as in 2030. Economic growth, mechanized transport, industrialization and the tendency to subsist on processed food are thought to be responsible for the significant rise of people being diagnosed with arterial hypertension, a condition in which the blood pressure in arteries is continuously elevated. (1, 2)

Arterial Hypertension is one of the biggest known risk factors for diseases, such as, stroke, coronary heart disease, heart failure, chronic kidney disease, peripheral vascular disease, and even dementia. It is therefore a dominant contributor to most of the deaths and disease burden worldwide. The two main causes of death alone, stroke and ischemic heart disease, respectively, are at fault for approximately 16 million deaths a year worldwide. (3, 4) While the African region has long struggled with infectious diseases and put most of its health-related resources in projects fighting these, a new, more silent killer has emerged during the last decade. In 2000 maternal, perinatal, and nutritional conditions were represented among the top 7 causes of death in the African continent – all communicable diseases. However, in 2016 a new trend emerged, stroke and ischaemic heart disease took the seventh and fourth place, respectively. (4)

Prevalence of arterial hypertension among the South African people has been described to be 35,1% but only half of them were aware of their elevated blood pressure levels. This indicates an immense percentage of undiagnosed and therefore untreated patients with hypertension in this region. (5) This trend seems consistently present in adolescence, with only limited data on prevalence and a high presumptive underdiagnosed disease burden. (6)

The first part of this thesis will give insights in physiological processes and regulatory mechanisms of the cardiovascular system in general and arterial blood pressure in particular. Subsequently the risk factors for developing arterial hypertension are being highlighted and available literature on disease burden of arterial hypertension in South Africa is summarized. Finally, the results from a cross-sectional study conducted in the

framework of this diploma thesis on the prevalence of arterial hypertension among adolescents in Mthatha, South Africa will be presented.

1.1 Cardiovascular System

A working cardiovascular system is essential for survival and is needed to supply tissues with adequate blood supply. It consists of the blood, blood vessels, and the heart. With its help oxygen (O_2) and vital nutrients are being brought to and waste products as well as CO_2 are being transported from all cells of the body. Not only does it have a supply and disposal function, but it is also essential for intercellular communication. Further, the cardiovascular system transports hormones from their place of creation to their place of effect. (7)

Circulating blood flow is a highly regulated physiological process. To fulfil all its purposes and to control the amount of blood that is being transported through the vessels the cardiovascular system depends on other organs. Primarily, adequate pumping function of the heart is of utmost importance but also the autonomic nervous system and the kidneys play an essential role in regulating the cardiovascular system. (7)

1.1.1 Systemic circulation

Systemic circulation starts when oxygenated blood leaves the left ventricle and is pumped into the aorta, the biggest artery in the body. From there the aorta branches and blood flows through the body within further arteries which decrease in diameter a little every time they branch out. Arteries get smaller, branch into arterioles and then they turn into capillaries. It is here, where blood exchanges substances like O_2 and CO_2 with the cells and surrounding tissue through a process called diffusion. Following the capillaries, deoxygenated blood is gathered within the venous system and is being brought back to the right heart ventricle. (7)

1.1.2 Pulmonary circulation

From the right heart deoxygenated blood flows through the pulmonary circulation and is being pumped through the pulmonary capillary network back into the left ventricle. In the lungs CO_2 leaves the blood and blood gets enriched with O_2 again. (7)

1.1.3 Systole and Diastole

Every physiological heartbeat consists of a systole and a diastole. During systole, the heart first goes through an isovolumetric phase, during which all valves of the heart are closed and pressure within the left and right ventricle rises. As soon as pressure inside the

ventricle exceeds pressure in the outflow tract (Aorta or truncus pulmonalis) the second phase of systole begins and blood flows through the aortic pulmonary valves into the systemic and pulmonary circulation system, respectively. The maximally reached pressure is referred to as SBP P_s. (7)

At the beginning of diastole myocardial contraction passes its peak and muscle cells of the heart, cardiomyocytes, start to relax again. As a result, pressure within left and right atrium declines until it falls below the outflow tract pressure. Consequently, the aortic and pulmonary valves will close again. Meanwhile, cardiac output undergoes sustained blood flow in the Aorta as the result of the Windkessel effect, relying on the aortas elasticity. (7) In this phase of blood circulation, arterial pressure falls to a minimum, referred to as DBP P_d. Consequently, the heart will receive new blood from the venous system and the whole process will start all over. (7)

1.1.4 Windkessel effect

The cardiovascular system of adults transports a total blood volume of about 5 litres. In children it is about 75-80 ml of blood/kg. With every beat, the left ventricle pumps about 70-80 ml of blood volume into the aorta. Since blood in the cardiovascular system is being pumped by the heart it does not flow continuously but thanks to the Windkessel effect blood does not stop flowing completely while the heart is in diastole.
Big arteries and the Aorta are particularly elastic, as they contain elastic fibres, called elastin. During systole, these elastic fibres stretch under volume strain and are capable of absorbing about half of the stroke volume and its corresponding energy that has been generated by the mechanical work of the mechanical contraction. In diastole, blood flow is sustained and is being transported further through recoil of these elastic arteries. This generates a more constant blood flow. Without the Windkessel effect, differences between systolic and DPB, also called the pulse pressure, would be much higher. (7)

The Windkessel effect deteriorates by age due to loss of elasticity in the big arteries. This happens because arterial walls like every kind of tissue in the body are in constant conversion. Elastic tissue gets replaced with collagen tissue thus lessening its mechanical compliance. With a reduced Windkessel effect, the heart has a to accelerate a taller blood column at once since the aorta cannot absorb the ejected blood volume and energy. Resultingly, the heart must overcome a higher amount of pressure to sustain circulation,

which consequently puts a considerable higher strain on cardiac structures. As an effect SBP is higher in people whose Aorta is low in compliance. (7)

1.1.5 Arterial Blood Pressure

The definition of arterial blood pressure is the current systolic and diastolic blood pressure in arteries in vicinity of the heart (e.g. Aorta). Measured of blood pressure is conducted in mm of mercury (mmHg), due to historical reasons. Arterial blood pressure undergoes constant temporal changes with every heartbeat. Physiologically, by the end of the cardiac filling phase, blood pressure lies at about 80 mmHg (DBP) and during cardiac contraction rises within 300 milliseconds to a systolic maximum value of 120 mmHg (SBP). Until the end of the upcoming diastole, blood pressure falls back to 80 mmHg. (7)

Mean arterial blood pressure is the driving force in the cardiovascular system, sustaining blood flow to the organs. In arteries around the heart mean arterial blood pressure can be calculated as the mean of systolic and DBP, with slightly lower levels observed in more distant arterial vessels. (7)

Figure 1 displays calculation of the mean arterial blood pressure based on cardiac output and total peripheral resistance. These two parameters themselves depend on the complex cooperation of multiple endocrine, neural, renal, local tissue, and vascular control systems. The amount of total peripheral resistance is largely determined by small arterioles and not by bigger arteries near the heart or the capillaries. Cardiac output is defined as the volume of blood the heart can pump in 1 minute. This is determined by preload, afterload, heart rate, and contractility. (8) (7)

$$MAP = CO \times TPR$$

Figure 1: Mean arterial pressure (MAP) can be calculated using only cardiac output (CO) and total peripheral resistance (TPR).

Arterial blood pressure levels do not stay constant throughout a day. It shows a biphasic course with two peaks, one early in the morning and one in the later afternoon. During night-time arterial blood pressure drops about 10-20 mmHg. This physiological decline is

often described as “dipper”. If the dip is missing, it can be a sign of secondary hypertension or sleep disturbances. (9)

1.1.6 Measuring arterial blood pressure

Arterial blood pressure can be measured indirectly or directly. The direct measurement of arterial blood pressure is performed by inserting a cannula connected to a pressure measuring instrument into an artery. A disadvantage of measuring arterial blood pressure directly is its invasiveness with the potential for procedural complications, such as infections, bleeding, or arterial aneurysms. Therefore, invasive arterial blood measurement is reserved to intensive medical care or cardiac catheterization.

The usual method used in everyday clinical practice is the indirect measurement of blood pressure not in the Aorta but in another main artery (e.g. brachial or femoral artery). It is illustrated in **Figure 2**. For this indirect method, a stethoscope and a manual blood measure cuff are utilized. To obtain valid results, correct placement of the patients’ arm at heart level is crucial. First the blood pressure cuff is put over the patients’ upper arm, encompassing it and is blown up. The pressure within the cuff should exceed the patients expected arterial blood pressure. This is verified by the absence of palpable radial arterial pulse distal to the cuff. Air is then being slowly released (2 – 4 mmHg/s). As soon as pressure of the blood pressure cuff lies below P_S Korotkoff sounds which sound like knocking noises can be heard with the stethoscope which is placed distal of the cuff on to the brachial artery. These sounds develop because blood can only flow during arterial pressure peaks into the vessel. When pressure within the cuff falls beneath $P_{D,}$ these sounds vanish. This indirect method was first described by Riva-Rocci, resulting in the referral of systolic and DBP in daily clinical practice as “RR” (e.g. in medical records: “RR 120/80”). (7)

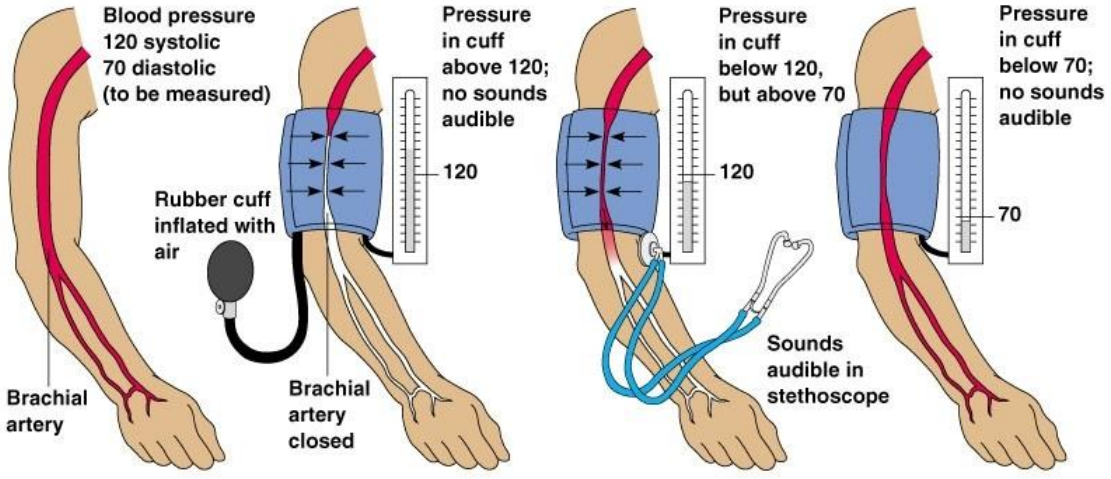

Figure 2: Blood pressure measurement with a sphygmomanometer. (10)

1.2 Systems regulating blood pressure

Various control systems are incorporated in regulating systemic blood pressure. All of them get feedback through various receptors located throughout the cardiovascular system. The term "feedback gain" can be used to express the respective effectiveness of a blood pressure control system. It is defined as the quantity of "correction" the system controlling blood pressure can provide split by the "error" that still persists after the initial shift in blood pressure. (11)

For example, if mean arterial blood pressure increases from 120 to 160 mmHg and any given control system returns it to 140 mmHg, -20 mmHg would be the correction and the resulting lasting overshoot in blood pressure would be +20. The gained feedback in this example would be -20/+20, or minus one, suggesting a negative feedback gain capable of correcting one half of the original disturbance in mean arterial blood pressure. A higher feedback gain indicates more physiological power of the control system. Every control system has a different feedback gain which itself is highly dependent on time. For example, following an abrupt drop in blood pressure due to sudden massive blood loss, the approximate response of the most important control systems is displayed in **Figure 3.** (12)

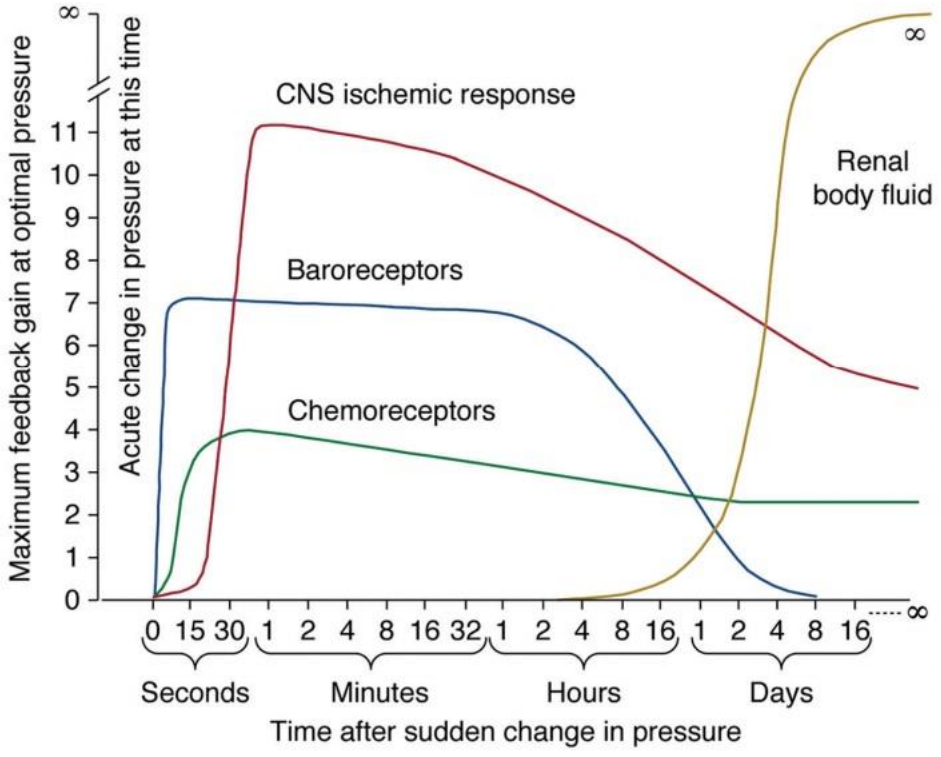

Figure 3: Time dependency of blood pressure control mechanisms. (12)

1.2.1 Short Term blood pressure regulation

Baroreceptors regulate arterial blood pressure in short term within seconds or minutes. Most of them are located in the aortic arch and the carotid sinus.

Baroreceptors and volume receptors not only monitor absolute pressure but also the velocity of pressure changes. They react to an increase in pressure and the associated stretching of vessels by the activation of afferent neurons via the vagus and glossopharyngeal nerves to the medulla oblongata. This leads to the subsequent activation of the parasympathetic nervous system and at the same time inhibits the sympathetic system. As a result, heart frequency, tone of the vascular walls and thus total peripheral resistance drop. Proximal vessels around the heart are now able to store more blood whereby contrary, central blood volume and stroke volume of the heart drops. These mechanisms result in a lower arterial blood pressure.

As baroreceptors adapt to different blood pressure levels within a few days they are not suited for a long-term blood regulation in contrast to volume receptors.

1.2.2 Mid and long-term blood pressure regulation

Long term regulation of blood pressure is physiologically controlled by the renal-body fluid regulating system. It is the only blood pressure control system that has almost unlimited feedback gain. Through absorption within the gastrointestinal tract, water and salt are constantly added to the extracellular fluid. To balance osmotic concentration of the extracellular fluid, constant monitoring of water and salt concentration and adoptive electrolyte excretion is conducted within the renal tubular system. Minor imbalances between output and intake can lead to big changes in extracellular volume and thus a potential change in blood pressure. It is even more important to maintain a physiological water and salt balance than to keep blood pressure within physiological boundaries. To maintain adequate blood flow for its regulatory functions, renal mechanisms can increase systemic blood pressure if its normal function is impaired. One of the key components for water and salt regulation is called pressure diuresis and natriuresis. Within this mechanism, the kidneys use the effect of a higher blood pressure to increase water and sodium excretion. A relevant feature of pressure natriuresis is that its effectiveness can be amplified or decreased depending on the input of various neural and hormonal systems. These tasks do not necessarily perform independent of each other as many physiological cascades run simultaneously, creating a complex interrelated system of blood pressure regulation. (13)

1.2.2.1 Chemoreceptors

Chemoreceptors mediate a nerval influence on the function of the kidneys. These receptors are located in the aortic arch and the carotid bifurcation. They monitor pH-value, carbon dioxide partial pressure (pCO2), and oxygen partial pressure (pO2). All values are being used for breathing regulation in the medulla oblongata on the one side, but also trigger afferent fibres of the sympathetic nervous system thus leading to a raise in cardiac output on the other side. (7)

1.2.2.2 Hormone Systems

At least three important hormone systems are of utmost importance in the regulation of the systemic blood pressure. **Antidiuretic hormone (ADH)**, also called vasopressin, is the central hormonal regulator of extracellular osmolarity. It is synthesized in the hypothalamus and is then released from vesicles of the posterior pituitary if extracellular fluid is hypertonic. ADH stimulates V_1-receptors located in smooth muscle cells of blood vessels, leading to vasoconstriction. As a result, total peripheral resistance increases. Furthermore V_2-receptors in the kidney cause incorporation of aquaporin-2 into the luminal surface of collecting tubules. This increases reabsorption of solute-free water into the circulation and thus influence tonicity of bodily fluids toward physiological levels. Half-life period of vasopressin is quite short and lies between 16-24 minutes. (14)

The hormone **atrial natriuretic peptide (ANP)** is released with increasing blood volume and blood pressure. Increased stretching of the atrium wall causes myocytes located in the atrium to release ANP. The main effect of ANP is to relax smooth muscle cells in arterioles especially those in renal preglomerular vessels. This leads to increased renal function and accompanying higher water and sodium chloride excretion. However, a significant increase in natriuresis can only be attained with stimulated renin-angiotensin aldosterone system (see below). Furthermore, ANP directly inhibits the excretion of aldosterone by affecting the adrenal cortex where it is being released and indirectly by inhibiting the release of renin.

The **renin-angiotensin aldosterone system (RAAS)** is a crucial hormone axis in blood pressure regulation and natrium homoeostasis. This axis is activated by insufficient renal blood flow. The hormone renin is then being released by juxtaglomerular cells in the kidneys. This is mediated (i) by the sympathetic system triggered by baroreceptors and (ii) the juxtaglomerular cells themselves, monitoring blood flow parameters indicating low

blood pressure. Renin converts angiotensinogen, released from the liver, to angiotensin I which is then being converted to angiotensin II by angiotensin-converting enzyme (ACE). Endothelial cells located in the lungs and the kidneys are crucial for this process due to their high activity of ACE. Angiotensin II has various effects in the body and interacts with angiotensin-II-receptors. In blood vessels, angiotensin II leads to the contraction of smooth muscle and thereby increases total peripheral resistance. In the central nervous system, angiotensin II triggers a sensation of thirst and craving for salt. Furthermore, angiotensin II additionally stimulates synthesis of aldosterone which increases renal sodium and water reabsorption. These mechanisms lead to an increase of intra-vascular volume, especially of the venous system which further increases cardiac output and thereby elevates systemic blood pressure. **Figure 4** provides an overview of the RAAS. (15)

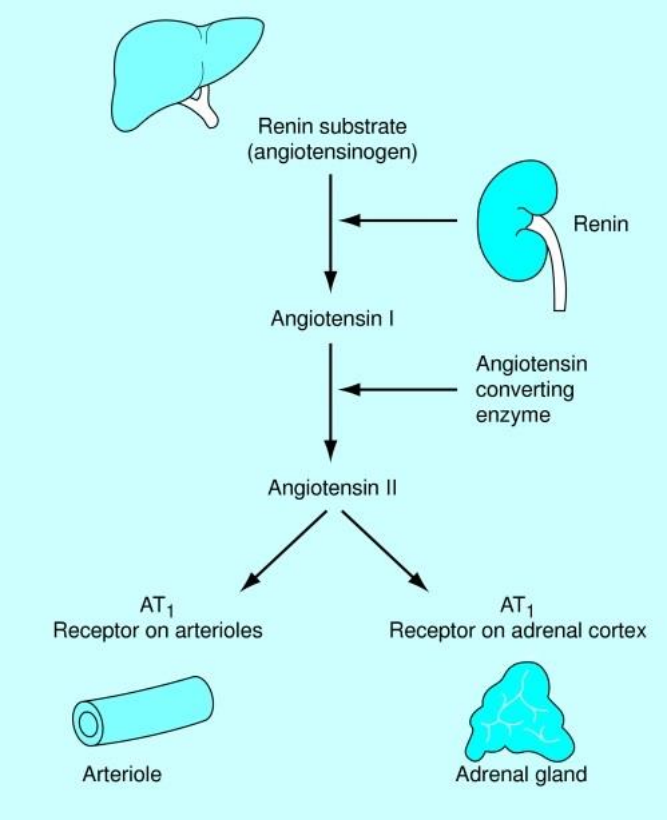

Figure 4: Renin-angiotensin system and effects on blood pressure and aldosterone release. (16)

1.3 Hypertension

1.3.1 Definition in adults

According to the European Society of Cardiology (ESC) 2018 guidelines arterial hypertension in adults is defined by a SBP higher than 140 mmHg and a DBP higher than 90 mmHg. An adult with SBP of 120-139 mmHg or a DBP of 80-89 mmHg is considered to have normal to high -normal blood pressure and therapeutic blood pressure controlled is not recommended. (17)

Everyone with a blood pressure below this threshold is considered to have an optimal blood pressure unless the patient shows symptoms of hypotension like dizziness, fainting, a feeling of light-headedness or blurred vision. (17)

Since the negative effect of blood pressure on the cardiovascular system is continuous, choosing a cut-off threshold for the distinction between hypertension and normotension is somewhat arbitrary. Nonetheless, in clinical practice the threshold named above simplifies diagnosis and guidance of subsequent treatment of hypertension. **Figure 5** summarizes the classification of hypertension according to ESC hypertension guideline. (17)

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension[b]	≥140	and	<90

Figure 5: Office blood pressure classification and hypertension grade definitions. (17)

1.3.2 Definition in children and adolescents

Since blood pressure depends on weight and maturity of a child, diagnostic criteria cannot be based on a generally valid blood pressure threshold to determine if the child is hypertensive. Therefore, hypertension in children is defined stratified by sex, height, and age. The US task force provides blood pressure percentiles for seven categories of height percentiles, both sexes, and for children aged from 1 to 17 years. They are displayed in **Figure 6** and **Figure** 7. (18)

SBP or DBP or both must be measured at least three times at or above the 95th percentile for height, age, and sex. If children have average systolic or DBP measurements between the 90th and 95th percentile for age, sex, and height, they get classified as having high-normal blood pressure. Due to pragmatic reasons, the definition of hypertension for adolescents over the age of 15 the definition of hypertension is not based on the 95th percentile. Rather, the ESC recommends that the absolute cut offs also used for adults should be used, as discussed above. (18)

If a child's blood pressure levels are between the 95th percentile and the 99th percentile, a diagnosis of stage I hypertension is made. Measurements above the 99th percentile plus 5 mmHg are classified as stage II. (18) Error! Reference source not found. summarizes categories of hypertension in adolescents. Figure 6 and figure 3 display the percentiles used for boys and girls by age and height, respectively.

Table 1: Classification of hypertension in adolescents and children. (19)

Category	0-15 years SBP and/or DBP percentile	16 years and older SBP and/or DBP values (mmHg)
Normal	<90th	<130/85
High normal	≥90th to <95th percentile	130-139/85-89
Hypertension	≥95th percentile	≥140/90
Stage I hypertension	95th to 99th percentile	140-159/90-99
Stage II hypertension	>99th percentile + 5 mmHg	160-179/100-109

Age (years)	BP percentile	SBP (mmHg) percentile of height							DBP (mmHg) percentile of height						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90
11	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

Figure 6: Blood pressure for boys by height and age percentiles. (19)

Age (years)	BP percentile	SBP (mmHg) percentile of height							DBP (mmHg) percentile of height						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88
11	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

Figure 7: Blood pressure for girls by height and age percentiles. (19)

1.3.3 Classification of arterial hypertension

High blood pressure is categorized by aetiology as primary hypertension (PH), also known as essential hypertension and secondary hypertension. 2% to 5% of all patients have known underlying adrenal or renal conditions that explain their hypertension. However, for most cases of arterial hypertension, no single identifiable cause can be identified. This sub-entity is classified as PH. (16)

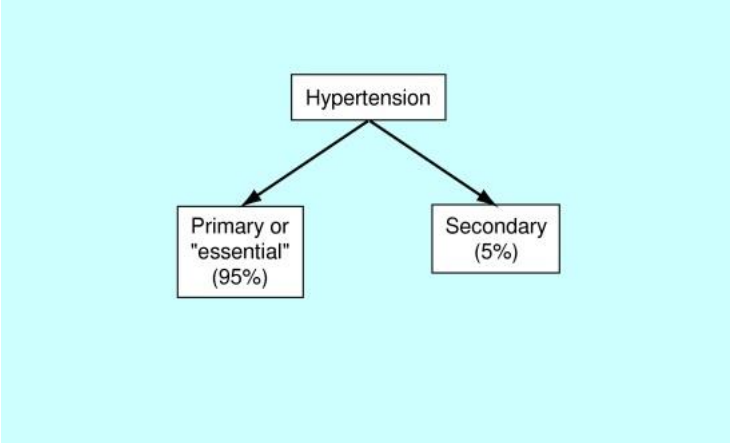

Figure 8: The relative frequency of primary and secondary hypertension. (16)

1.3.4 Pathophysiology of primary hypertension

The pathophysiology of PH remains uncertain and a matter of debate. It seems that no single cause is responsible to cause PH alone, suggesting a multifactorial aetiology. As stated above, the maintenance of physiological blood pressure is regulated by various mechanisms. A derangement of these may play a crucial part in the pathophysiology of PH. Different risk factors, which are thoroughly discussed later, lead to endothelial dysfunction and an altered response especially of the renin-angiotensin system and the sympathetic nervous system. (20)

1.3.4.1 Peripheral resistance and cardiac output

The main factors for blood pressure are cardiac output and peripheral vascular resistance. In many patients with PH, cardiac output is normal, but their peripheral resistance is raised. Since small arterioles make up most of the total peripheral resistance, they have been studied quite extensively. Smooth muscle cells in the walls of arterioles can contract to reduce blood flow. During contraction, intracellular calcium concentration is thought to rise because drugs blocking calcium channels have been observed to have a vasodilatory effect. A hypothesis is that prolonged constriction of those smooth muscle cells leads to structural changes and subsequently induce a thickening of the walls of arterial vessels that is further induced by angiotensin. All of this is thought to contribute to a steady rise in total peripheral resistance, contributing to arterial hypertension. (16)

1.3.4.2 Renin-angiotensin system

One of the most crucial endocrine system controlling blood pressure is the RAAS. Angiotensin II causes vasoconstriction and is a stimulant to the release of aldosterone, which further raises blood pressure by increasing blood volume. Despite all this it is still not clear whether the renin-angiotensin system is directly related to elevated blood pressure in PH. Especially in the Afro-American population and elderly patients with PH, low blood levels of angiotensin II and renin have been observed and no adequate response to RAAS-inhibitors for lowering of blood pressure has been achieved. However, several studies support the concept that there are several important “local” non-circulating renin-angiotensin paracrine or epicrine effects, which also control blood pressure. It has been reported that there are local renin systems in the heart, the arterial tree, and the kidneys that could have important influence in how blood flow is regulated regionally, raising the question of a potential pathophysiological link to PH. (16) (21)

1.3.4.3 Autonomic nervous system

Both arteriolar dilatation and arteriolar constriction can be caused by the sympathetic nervous system. This is crucial for blood pressure regulation, especially for changes in the short term. However, studies have found little evidence that epinephrine or norepinephrine play any significant role in the aetiology of PH. Nevertheless, the sympathetic nervous system can be inhibited by drugs which are known to decrease blood pressure and are well established in daily clinical practice, so their effects should not be disregarded.
It has been suggested that the renin-angiotensin system and the autonomic nervous system interact with each other and thereby lead to PH. Furthermore, other factors including circulating volume, sodium and other hormones could influence each other and thereby play a role in the pathophysiology of PH but further research on this issue needs to be conducted. (22)

Furthermore, experts found that hypertension was maximally associated with sympathetic overactivity, suggesting a disturbance in basal sympathetic tone which arises from the hypothalamus. (20)

1.3.4.4 Endothelial dysfunction

Vascular endothelial cells secrete many locally acting vasoactive agents. These include, amongst others, endothelin, a vasoconstrictor peptide, and nitric oxide, a vasodilator molecule. These molecules seem crucial in cardiovascular regulation and a dysfunction of the endothelium seems to be linked to PH. (23)

The aim of numerous studies is to modulate endothelial function and thereby understand and minimize the complications of PH. Antihypertensive therapy that is proven to be clinically effective and has been shown to normalize concentrations of nitric oxide but restoration of a physiological response of endothelium to the presence of endothelial agonists has been futile. This seems to indicate the irreversibility of the hypertensive process so that the endothelial dysfunction can be classified as primary. (23)

1.3.4.5 Vasoactive substances

Many other mechanisms and vasoactive systems that affect vascular tone and sodium transport regulate physiological levels of blood pressure. However, studies could not exactly determine how they are involved in the exact process leading to PH yet. (16)

Bradykinin is one of the vasoactive substances that leads to vasodilatation. ACE inactivates bradykinin and therefore the effect of drugs like ACE inhibitors may block bradykinin inactivation, helping to slow down development of PH. (24)

Endothelin-1 is an endothelial vasoconstrictor that has been recently discovered. It is assumed to increase salt sensitivity and consequently raise blood pressure. Furthermore, endothelin-1 activates locally acting renin-angiotensin systems. It has been demonstrated in genetically modified mice that endothelin-1 is involved in causing vascular disease and influence regulation of blood pressure levels. (25)

Venous and arterial endothelium produces **nitric oxide (NO)**, formally known as endothelial derived relaxant factor. This molecule diffuses into the smooth muscle cells through the vessel wall and causes vasodilation. Studies suggest that impaired NO bioactivity plays a crucial role in the development of PH. (26)

NO synthesis is also thought to be impaired in patients with PH. The lower concentration of NO leads to a higher sensitivity to vasoconstrictors and increases renal vascular resistance either directly or by making the renal vessels more responsive to vasoconstrictors like angiotensin II. (27)

Atrial natriuretic peptide is also suspected to influence the pathophysiology of PH. A defect in its physiological role to excrete water and sodium may contribute to PH by increased extracellular volume. Furthermore, its interaction with the RAAS appears to be of key value to understand the exact pathophysiology and needs further investigations. (28) (29)

1.3.5 Risk factors for developing primary hypertension

In the past, many misconceptions were held regarding high blood pressure. For example, it was believed that women are not negatively affected by high blood pressure and that it was an increase of blood pressure with age was a physiological phenomenon. Historically, the Framingham Heart Study was the first large-scale cohort study starting in 1948 to determine cardiovascular risk factors and laid the foundation about key factors of our understanding of CVDs including hypertension and etiological contributors. It was also the Framingham Heart Study that introduced the term "risk factor".
However, as of today, studies have not yet been able to identify a single essential risk factor that leads to PH. In fact multiple studies indicate that a combination of factors that are linked to each other are promoting higher risk to develop arterial hypertension. (30) (12)

Risk factors can be split into modifiable and non-modifiable risk factors. Non modifiable risk factors are characteristics or attributes that the individual cannot alter or adjust, therefore there is no possibility to change them, either by the individual or modern medicine. These factors include genetic composition, race, family history, sex, age, etc. Risk factors that are modifiable, in turn, are characteristics, lifestyle patterns or exposure to certain agents that the individual can control or change to prevent outbreak of the illness or delay its onset. The most common modifiable risk factors probably leading to arterial hypertension include physical inactivity, obesity, diabetes mellitus and ex-smoking, others are excessive salt intake, high fat diet and alcohol consumption. Error! Reference source not found. lists the modifiable and non-modifiable risk factors highlighted in the 2018 ESC/ESH guidelines for the management of arterial hypertension. (31) (32)

Most importantly, the development of arterial blood pressure physiologically heavily depends on age. Starting from an arterial blood pressure of 75/50 mmHg in a newborn, it continuously increases and reaches a plateau of about 120/80 mmHg in healthy 20 to 40-year-olds. Due to a decrease in elasticity of vessels, SBP raises steadily. This factor is further highly dependent on underlying genetic factors and is currently under thorough investigation. Many susceptible genes thought responsible to cause hypertension are under investigation (33) (34)

Since 20% of cases of EH occur as isolated diseases in otherwise healthy patients, all other cases occur concurrently with other metabolically related diseases and conditions. These comorbidities include obesity, insulin resistance or glucose intolerance, left ventricular hypertrophy and dyslipidaemia. A patient has a four times higher rate to develop hypertension if three or more of the risk factors listed above are presenting in an individual. (35)

Further, genetic, and epigenetic influences effect the development of PH. One study found 11 genetic markers thought to be in association with PH. Many genes are already known to have a specific phenotypic relationship or to be associated with other genes related to PH. Others influence already established physiologic pathways known to be associated with PH. (36)

Several studies conducted have shown that women under the age of 65 have a lower prevalence of arterial hypertension compared to men of the same age. Differences in hypertension in human and animal populations are contributed to behavioural and biological factors. In general, men seem to have higher blood pressure compared to women. This seems to be independent of race and ethnicity. (37) (38)

Especially obesity has been reported in several studies to be increasingly co-existent with PH. More precisely, it has been shown that body fat stored centrally is a more accurate determinant of higher blood pressure than peripheral body fat. Overall, obese patients have a 3.5 – fold increased likelihood to have arterial hypertension. (39) (40)

Obstructive sleep apnoea (OSA) is a common persistent disorder characterized by ongoing events with a limited or total collapse of the upper airway while the individual is asleep. This causes reduction or cessation of the airflow causing progressive asphyxia It is a disease closely associated with obesity and arterial hypertension. Over 69% of individuals with OSA are obese and weight loss has shown to reduce the symptoms of OSA. (41) OSA is also considered a risk factor for arterial hypertension, so weight management is crucial for individuals with elevated blood pressure.

Finally, physical activity seems to have great influence on blood pressure. Numerous randomized controlled trials confirmed that physical activity leads do a decrease in blood

pressure. The effect seems to be greater in individuals diagnosed with hypertension than in individuals that have physiological blood pressure levels. It is still not exactly known which mechanisms lead to reduction of BP. (42) Evidence suggests that it is not important, which kind of physical activity is being carried out. A study analysing the effects of dynamic resistance, endurance, combined resistance and endurance training, and isometric resistance training found that all forms of training lower resting blood pressure levels in participants. The largest reduction of SBP was found to be the result of isometric resistance training, although there exists only limited data. (43)

Table 2: Modifiable and non-modifiable risk factors. (17)

Modifiable risk factors	Non-modifiable risk factors
Current or past history of Smoking	Sex (men > women)
Total cholesterol and HDL-C	Age
Physical inactivity	Race
Overweight or obesity	Uric acid
Sedentary lifestyle	Diabetes
Socioeconomic and psychosocial factors	Family history of premature CVD
Heart rate (resting values >80 beats/min)	Family or parental history of early-onset hypertension
	Early-onset menopause
	Established CV or renal disease

Another risk factor to have arterial hypertension in adulthood is to already have it diagnosed during childhood. (44) Obese children have the highest risk of developing arterial hypertension, other factors include family history and male sex of hypertension. (45) Furthermore, children born prior to date of birth estimated by a doctor, are overweight or of African-American descent and small for gestational age have a higher risk for development of arterial hypertension. (46)

1.3.6 Clinical Picture

Patients with elevated blood pressure usually do not report symptoms. Symptoms are only showing if target organs are affected. The organ systems most affected from end organ damage are the brain, the kidneys, and the heart. If the brain is affected, it can lead to blurry vision, headaches, dizziness, cognitive impairment, and stroke. Hypertensive damage of the heart can lead to symptoms like chest pains, shortness of breath, palpitations, arrhythmia, circulatory collapse, and signs of heart failure. A damaged kidney

can lead to polyuria and thus to thirst, nocturia, haematuria and urinary tract infections. (17)

Though, when individuals are brought to attention that they have arterial hypertension and are asked to report them, about half of the patients can tell when they have a spike in blood pressure. Further symptoms included nervousness, tachycardia and rubefaction. (47)

1.3.7 Consequences of chronic arterial hypertension

Arterial hypertension doubles the risk in patients for development or progression of coronary heart disease, chronic heart failure, cerebral haemorrhagic and ischemic cerebral, chronic kidney disease, stroke and peripheral arterial occlusive disease. In many patients hypertension often is not the only cardiovascular risk factor present. This leads to an even higher overall risk. (48)

1.3.8 Treatment

An efficient therapy of hypertension is proven to reduce the number of cases of cardiovascular and renal disease. Already a 10-mmHg reduction of SBP or a reduction of 5 mmHg in DBP reduces the number of cardiovascular events and reduces mortality significantly. Still most patients are being treated insufficiently or get no treatment at all, either due to underdiagnosis or a lack of disease awareness in patients that has a negative effect on therapy adherence. (49) (50)

1.3.8.1 Lifestyle modifications

Change in lifestyle can delay onset of hypertension or lead to a reduction of blood pressure. (51) Patients with grade 1 hypertension could also use lifestyle modifications instead of relying on drug therapy. Lifestyle modifications also enhance the effects of blood pressure lowering therapy, although they should not be used as a substitute for drug therapy in patients with hypertension-mediated organ damage (HMOD) or at a high risk of CVD. (52) (53) Poor persistence of patients to a change in lifestyle over time is a considerable factor to consider. In one study it was low where adherence to lifestyle modification was only 23%. (54)

Recommended lifestyle modifications proven to lower blood pressure are, high consumption of vegetables and fruits, salt restriction, weight reduction and regular physical activity, moderation of alcohol consumption, and maintaining an ideal body weight. (17) Furthermore, smoking has shown to have a prolonged effect on blood vessels causing vasoconstriction. This is thought to contribute to raise daytime ambulatory blood pressure. Not only regarding blood pressure but for prevention of cancer or other CVDs smoking cessation should be seriously taken into consideration by every smoker. (55)

1.3.8.2 Pharmacological therapy

To achieve optimal blood pressure levels, most patients require pharmacological therapy. There exist five major drug classes that are in daily clinical use to treat arterial hypertension. Their effectiveness has been verified by many meta-analyses. (56) (57)

- Angiotensin-converting enzyme inhibitors (ARBs)
- Angiotensin receptor blockers or Angiotensin-converting enzyme inhibitor (ACEi)
- Calcium channel blockers (CCBs)
- Thiazide/thiazide-like diuretics
- Beta-blockers

Other antihypertensive drugs were used in the earlies years of antihypertensive treatment when other drugs were not discovered yet. The effectiveness of certain alpha-blockers was better than that of placebos, but spironolactone was even more effective. (58)

In most patients, therapy with just one antihypertensive drug (monotherapy) is not sufficient. Even when the administered dose of a single drug reaches its maximum, additional blood pressure lowering is very little, compared to the initial dose. Administering a drug in a higher dose also can lead to more adverse effects. This was the reasoning to change initial treatment of hypertension for most patients. The initial treatment in today's guidelines is a combination of two substances, combined in one pill, also called single-pill combination (SPC). Excluded are patients with high-normal blood pressure and frail older patients, who still should get monotherapy as initial treatment. (17)

Figure 9: Core drug treatment strategy for uncomplicated hypertension. displays the treatment algorithm for patients with uncomplicated hypertension. This includes

individuals with no other underlying disease other than hypertension, patients with (HMOD), diabetes, cerebrovascular diseases, or peripheral artery disease. (17)

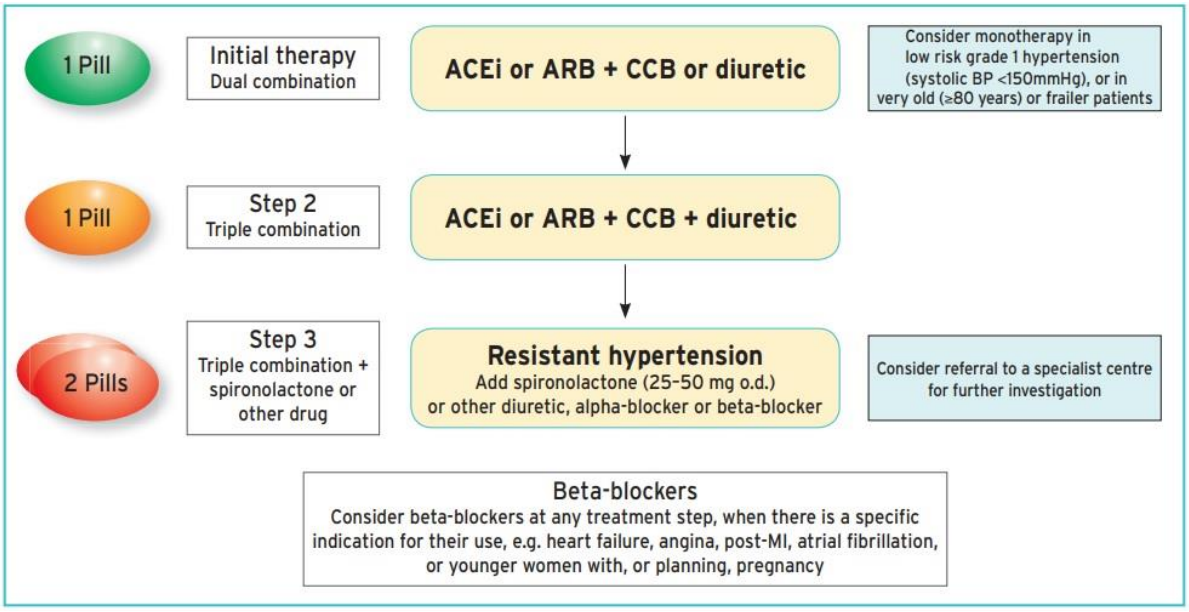

Figure 9: Core drug treatment strategy for uncomplicated hypertension. (17)

Hypertension can be the only illness present in many otherwise healthy patients. However, many patients suffer from other diseases, making it essential to adapt drug therapy to each individual and taking their medical history into consideration, since studies found that there are different outcomes in treatment if a different disease was present. Therefore, different algorithms have been developed, depending which disease is present together with hypertension. (17)

Four underlying disease make it necessary, to choose a different algorithm than the one for treatment for uncomplicated hypertension:

- Coronary artery disease
- Chronic kidney disease
- Heart failure with reduced ejection fraction
- Atrial fibrillation

Figures Figure 10 to **Figure** 11 display the drug treatment algorithm for patients with coronary artery disease, chronic kidney disease, heart failure with reduced ejection fraction, and atrial fibrillation.

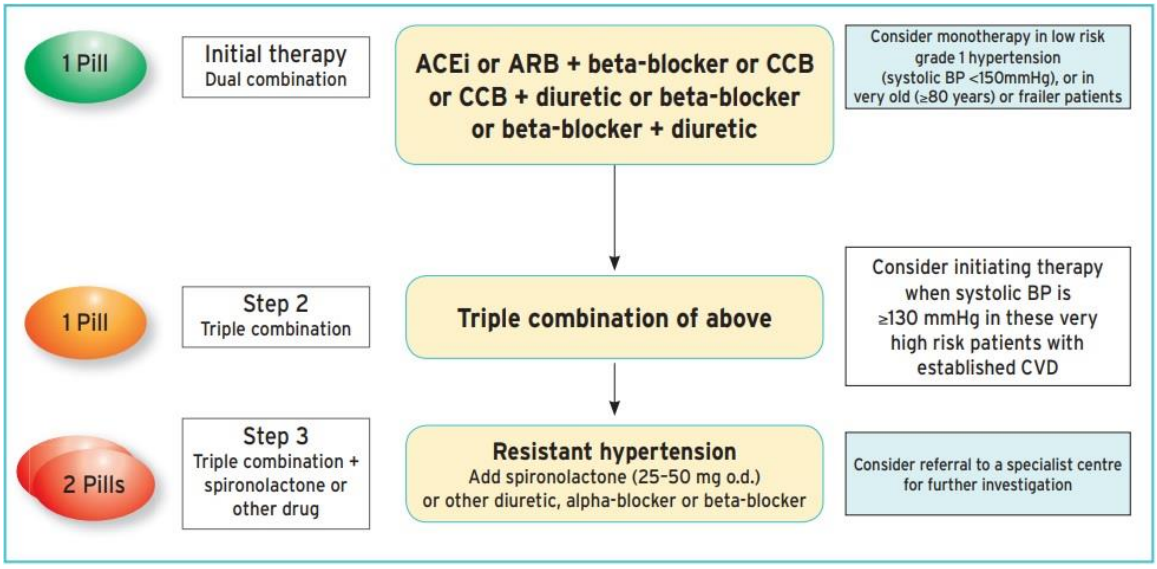

Figure 10: Drug treatment strategy for hypertension and coronary artery disease. (17)

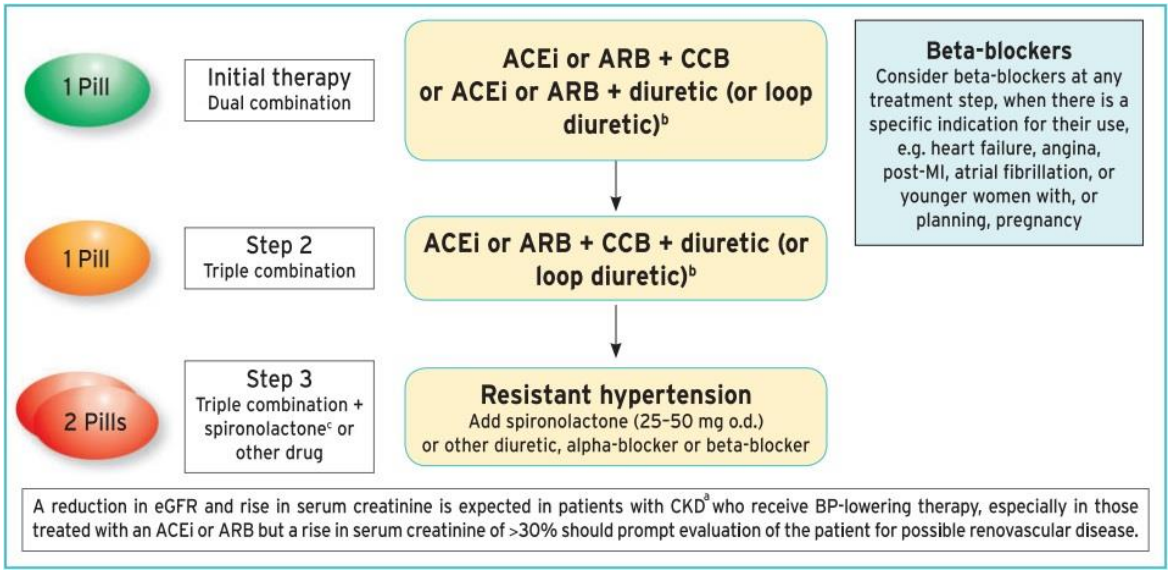

Figure 11: Drug treatment strategy for hypertension and chronic kidney disease. (17)

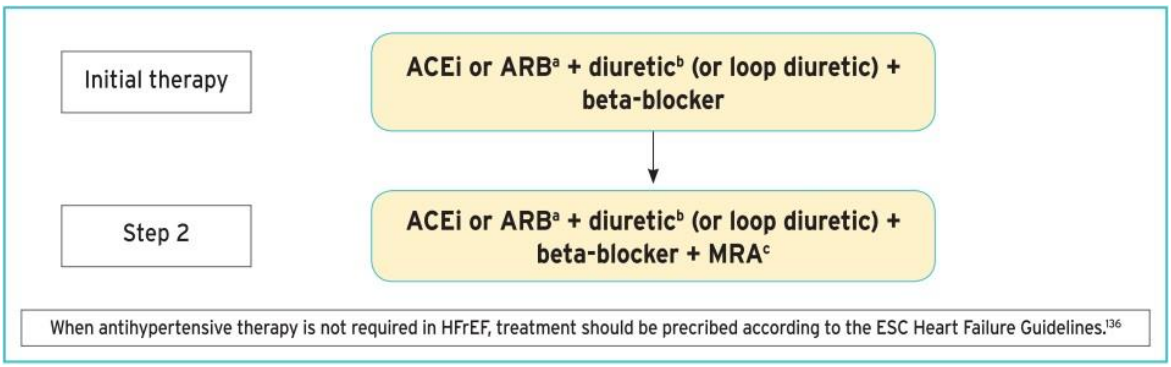

Figure 12: Drug treatment strategy for patients with heart failure with reduced ejection fraction and hypertension. (17)

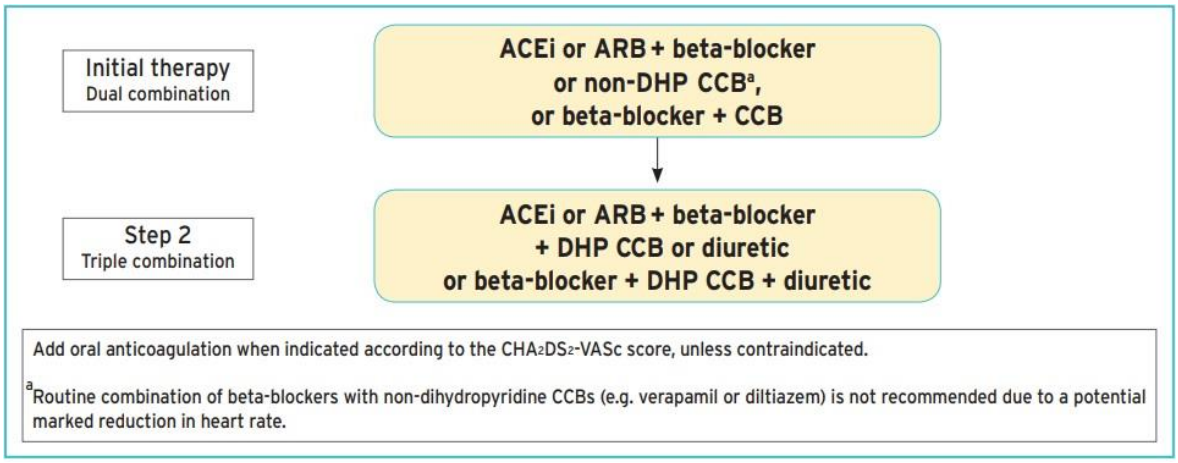

Figure 11: Drug treatment strategy for patients with atrial fibrillation and hypertension. (17)

1.3.9 Epidemiology

The estimated worldwide prevalence of pre-hypertension and hypertension in 2000 was over a quarter (26%) of the adult population. According to projections for the year 2025 this would rise by 24% in western countries and 80% in third world countries. A Canadian population-based study examining the prevalence of diabetes mellitus found that the prevalence in 2005 already reached levels predicted for the year 2030. These findings indicate an even higher prevalence of hypertension than predicted in 2025. (2) (59)
This trend has been associated to the fact that people are massively changing their lifestyle and the incidence of obesity is increasing. (60)

Experts found that a reduction of only 2-mmHg in a community's mean DBP could decrease the prevalence of hypertension by 17%, indicating that even modest changes in lifestyle could have tremendous public health implications. (61)

As shown by recent studies, only about 40% of patients affected by hypertension are getting treatment. Of these, only about 35% have regular control measurements, making sure their blood pressure stays under 140/90 mmHg. This seems to be the case, regardless of world region, the level of development of healthcare system or whether it is a high- or low-income country. (62)

1.3.9.1 Prevalence of arterial hypertension in developed countries

Age specific mean arterial blood pressure cut-off values and prevalence of arterial hypertension vary between and within countries. Except for very few culturally isolated populations in developing countries, arterial hypertension can be found in all population groups globally. In developed nations, blood pressure rises continuously until the age of 20. This increase during childhood and adolescence is a sign of overall growth and maturity. In the US, young men have more elevated mean SBP compared to women who are the same age. At the same time, female mean blood pressure rises quicker during advanced age than in men. Accordingly, starting from around 60 years of age women on average lean to have greater mean blood pressure than males the same age. DBP rises continuously as well, reaching its peak around the age of 55. From that moment DBP decreases, leading to an increased pulse pressure. (63)

In the US about 65 million people or 30% of the population are diagnosed with arterial hypertension (defined by at least of the following criteria: SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, receiving hypertensive treatment). The prevalence among the African American community is 33,5%, in whites 28,9% and in Americans with Hispanic origin 20,7%. In people over 60 years of age, prevalence rises to 65,4%. Further studies suggest a rising total prevalence in the population of the US, with hyperalimentation being discussed as a possible cause. (63)

In the African American population, hypertension manifests earlier compared to the remainder of the population. This is accompanied by a higher degree of severity as well as higher morbidity and mortality due to coronary heart disease, stroke, left ventricular hypertension, and terminal kidney failure. (64)

Genetic and environmental factors have been implicated to contribute to regional and ethnic differences in physiological blood pressure. For example, migration analysis of relocation into a more urban environment has shown to raise blood pressure significantly. (63)

1.3.9.2 Prevalence of arterial hypertension among adults in South Africa

A study concluded in 2012 by the South African General Household Survey (GHS) found that the prevalence of hypertension among adults in South Africa was 10,4%. It increased as the study participants got older, independent of race. Individuals aged 65 and older had a prevalence of 40% and individuals aged 40 to 50 years had a prevalence of about 10%. Women had a higher prevalence of arterial hypertension than men in almost every age group, except for 18-24 years. A similar study of 2003 was also conducted by the GHS had the result of a prevalence of about 15% and in 1998 the reported prevalence was 12%. However, since the data of the DHS was self-reported, there have been growing concerns about the data quality provided by the DHS. In one study the prevalence of women was double that of men and in the other one it was vice versa. This led to many concerns about the quality of the blood pressure data provided by the DHS. Also, the number of hypertensive people that took antihypertensive treatment was over 90%. The authors of this study doubt that the number of patients getting medical treatment is that high in South Africa. (65) (66) (67)

1.3.9.3 Prevalence of arterial hypertension among adolescents in South Africa

Worldwide the prevalence of arterial hypertension amid adolescents under the age of 18 has been shown to be 1-5%, the prevalence of pre-hypertension was 9.7%. During the last two decades a trend of rising prevalence in arterial hypertension in adolescents and children was observable. (68) (69)

Studies examining the prevalence of arterial pre-hypertension and hypertension amidst adolescents in South Africa had results varying from 13% and 14% to 21% and 29%, respectively, in children of African ancestry. (44) (70)

1.4 Aims and Objective

As described above PH is known to be a public health problem in developing and developed countries. However, developing countries are relatively new to the issue of non-communicable diseases. Therefore, as much data as possible about its prevalence is needed. This, in turn, is essential for policy makers to make informed public health decisions on how to ward a possible oncoming epidemic of arterial hypertension off. (71) The presumption is that there is a high prevalence in hypertension in underdeveloped regions of South Africa and that arterial hypertension often goes underdiagnosed. Data from other developing countries show that the prevalence of arterial hypertension in high school children in India is over 5% and publications from Sudan report a prevalence of 9%. (72) (73) Other studies conducted in South Africa give reason to believe that the trend to increasing rates of hypertension remains intact. (70) To what extent remains to be seen. Therefore, we have chosen to conduct this study in Mthatha, South Africa. It is a city in the district of the Eastern Cape with the lowest Human Development Index. Since early recognition and treatment is the most competent way to limit the harmful long-term effects of raised blood pressure, assessing the prevalence of arterial hypertension could be very useful.

The aim of this thesis is to empirically assess to which extend adolescents in underdeveloped and therefore more rural regions of South Africa are at risk of arterial hypertension and other factors associated with it. Therefore, arterial blood pressure measurements from children aged 13-16 years old from schools around Mthatha, South Africa, were taken to assess the prevalence of hypertension in this cohort. Furthermore, weight and height measurements were taken to assess the relationship between arterial hypertension and obesity.

2 Materials und Methods

2.1 Study design

High school students in and around Mthatha, Eastern Cape Province, South Africa, were selected for a cross-sectional cohort study. The participants were aged 13-16 years and females and males.

2.2 Inclusion/exclusion criteria

Inclusion criteria were female or male adolescents of African descent and aged 13-16 years. Participants had to be free from any renal, pulmonary, orthopaedic, or chronic vascular diseases.

Exclusion criteria comprise the students being acutely ill, pregnant, lactating, or physically challenged to the extent that collection of anthropometric data was hindered. Further, individuals on blood pressure-lowering medication, or with any self-reported comorbidity or endocrinological or cardiovascular disorder and of non-African descent were excluded from participation.

2.3 Ethics approval

National and local regulations in South Africa were considered and the Health Sciences Ethics Committee of Walter Sisulu University, South Africa (Ref No: 045/2018) gave its ethic approval. After the aims and methods of the study were thoroughly explained to the students verbally, it was necessary for the parents or legal guardians to submit a written informed consent, stating that they and the adolescents understood the aims and methods of the study and agreed to participate in it voluntarily.

No considerable changes in method were conducted after the initiation of the study.

2.4 Blood pressure measurements

Before blood pressure measurements were taken, individuals were seated for 5 minutes in a quiet room to prevent confounding influences of physical and mental activity. A calibrated Omron automated sphygmomanometer (HBP-1100; Omron Healthcare Co. Ltd.) was used to quantify the participants´ arterial blood pressure. An arm-size appropriate cuff was applied to the upper right arm and blood pressure was taken three times with a break of 2 minutes between measurements. The mean value of the readings was used for analyses. By classifying the average value within blood pressure percentiles according to height, sex and age the individuals were stratified as normotensive (systolic blood pressure (SBP) and

diastolic blood pressure (DBP) < 90th percentile), pre-hypertensive (SBP and DBP > 90th < 95th percentile or SBP/DBP ≥ 120/80 mmHg) or hypertensive (SBP and/ or DBP ≥ 95th percentile) according to the 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. (55) The mean arterial pressure (MAP) was calculated using following formula: MAP = (SBP + (2 x DBP))/3.

2.5 Weight and height measurements

A Tanita body composition scale was used to measure weight. For height measurements all students had to be barefoot. A wall-mounted Harpenden stadiometer was used to measure height which was recorded to the nearest 0.1cm. BMI was calculated using the formula: BMI = weight (kg) / [height (m)]^2. Individuals were grouped into four different weight status categories (Underweight, Healthy weight, Overweight, and Obese) using the definition by the US Preventive Services Task Force. Herby percentile curves were used to classify BMI as follows: Underweight: < 5th percentile, Healthy weight: > 5th < 85th percentile, Overweight: ≥ 85th < 95th percentile and Obese: ≥ 95th percentile. (74)

2.6 Statistical analysis

All statistical analyses were performed with the commercially available package STATA 15.0 (Stata Corp., Houston, TX, USA).Standard statistic descriptions have been used to summarize cohort specific characteristics such as median and corresponding interquartile-range, mean and standard deviation or percentages, as appropriate. Differences between groups were evaluated by students t-test for normally distributed continuous data with graphical assessment of normality, or chi^2-test for categorical data. Binary logistic regression was used to estimate the association between BMI and elevated blood pressure.

3 Results

3.1 Baseline characteristics of study cohort

Data was obtained from a total of 244 students within the present cross-sectional study cohort. Median age of the cohort was 14 years (mean: 14,4 (SD 1.0)) and 77.05% were females (n=188). Median BMI was 20.6 (mean 20.6 (SD4.8)) and 15.6% of students were found to fulfil criteria for obesity (n=38) and 16% of students for overweight (n=39). Median SBP in the overall cohort was 115.7 mmHg (IQR: 107.2 – 122.3), median DBP was 72.3 mmHg (IQR: 67.7 – 78.2 mmHg) and mean arterial blood pressure was 87.1 (IQR: 81.3 – 91.9). Displayed in **Table 3** are the baseline characteristics of the study cohort.

Furthermore absolute systolic and DBP values stratified by sex are displayed in **Figure 12**. SBP and DBP for females was 114.5 mmHg (mean 114.9 (SD 12.0)) and 73.2mmHg (mean 73.6 (SD 7.7)), respectively, and SBP and DBP for males was 116.5 mmHg (mean 117.3 (SD 11.5)) and 70.3 mmHg (mean 70.5 (SD 8.7)).

Table 3: Demographics and clinical characteristics.

Variable	n (% missing)	Mean (standard deviation)
Age (years)	244 (0%)	mean 14.4 (SD +-1.0)
Female	244 (0%)	188 (77.1%)
Male	244 (0%)	56 (22.9%)
BMI (kg/m²)	244 (0%)	mean 22.0 (SD 4.8)
Obese*	244 (0%)	38 (15.6%)
Overweight*	244 (0%)	39 (16.0%)
Systolic blood pressure (mmHg)	244 (0%)	mean: 115.5 (SD 11.9)
Diastolic blood pressure (mmHg)	244 (0%)	mean: 72.9 (SD 8.1)
Mean arterial pressure (mmHg)	244 (0%)	mean: 87.1 (SD: 8.1)

***defined as an age- and sex-specific BMI in the 85th to 94th percentile**

** defined as an age- and sex-specific BMI over the 95th percentile

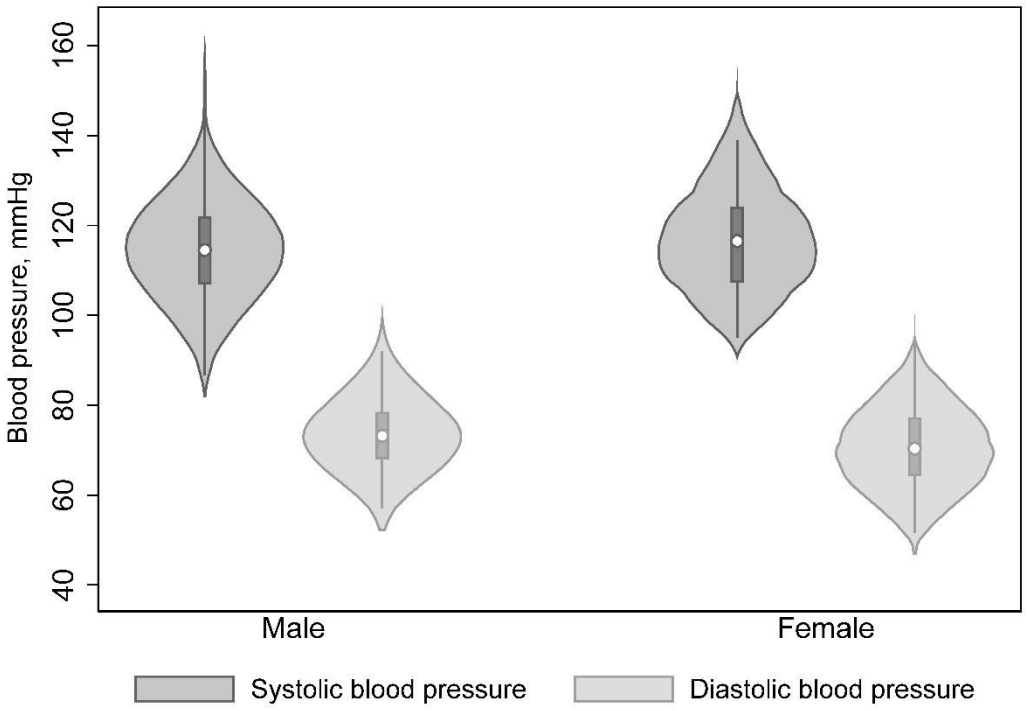

Figure 12: Absolute systolic and diastolic blood pressure values by sex.

3.2 Prevalence of arterial hypertension

The prevalence of PHT (SBP and DBP between 90th and 95th percentile for sex, height, and age or SBP/DBP ≥ 120/80 mmHg) in the study sample was 15,6%, the prevalence of HT (SBP and/ or DBP ≥ 95th percentile for sex, height, and age) was 23.4%. A total of 95 (38.9%) out of 244 study participants had elevated blood pressure levels. All numbers are displayed in **Table 4**.

Table 4: Prevalence of arterial hypertension.

Variable	n (% missing)	count (%)
Normotensive	244 (0%)	139 (57%)
Pre-hypertensive	244 (0%)	38 (15.6%)
Hypertensive	244 (0%)	57 (23.4%)
PHT and HT combined (elevated blood pressure)	244 (0%)	95 (38.9%)
Systolic BP		
Normotensive	244 (0%)	185 (75,8%)
Pre-hypertensive	244 (0%)	19 (7.8%)
Hypertensive	244 (0%)	40 (16.4%)
Diastolic BP		
Normotensive	244 (0%)	179 (73,4%)
Pre-hypertensive	244 (0%)	32 (13.1%)
Hypertensive	244 (0%)	33 (13.5%)

Normotensive, <90th percentile; PHT, ≥90th percentile and <95th percentile; HT, ≥95th percentile.

Of 188 females included in the study, 54 (23.9%) fulfilled criteria for elevated DBP (26 with pre-hypertensive DBP, 28 with hypertensive DBP). 46 (24.5%) fulfilled criteria for SBP (14 with pre-hypertensive SBP, 32 with hypertensive SBP). Detailed results of blood pressure categories in females are summarized in Table 5: Hypertension prevalence data for females.**Table 5**.

Of 56 male participants, 11 (19,6%) fulfilled criteria for elevated DBP (6 with pre-hypertensive DBP, 5 with hypertensive DBP). 13 (23.2%) fulfilled criteria for SBP (14 with pre-hypertensive SBP, 32 with hypertensive SBP). Detailed results of blood pressure categories in females are summarized in **Table 6**.

Table 5: Hypertension prevalence data for females.

		Diastolic blood pressure			
		Normotensive, n	Pre-hypertensive, n	Hypertensive, n	Total, n (%)
Systolic blood pressure	Normotensive, n	113	18	11	142 (75.53%)
	Pre-hypertensive, n	10	2	2	14 (7.45%)
	Hypertensive, n	11	6	15	32 (17.02%)
	Total, n (%)	134 (71.28%)	26 (13.83%)	28 (14.89%)	188 (100%)

Normotensive, <90th percentile; PHT, ≥90th percentile and <95th percentile; HT, ≥95th percentile.

Table 6: Hypertension prevalence data for males.

		Diastolic blood pressure			
		Normotensive, n	Pre-hypertensive, n	Hypertensive, n	Total, n (%)
Systolic blood pressure	Normotensive, n	36	3	4	43 (76.79%)
	Pre-hypertensive, n	4	1	0	5 (8.93%)
	Hypertensive, n	5	2	1	8 (14.28%)
	Total, n (%)	45 (80.36%)	6 (10.71%)	5 (8.93%)	56 (100%)

Normotensive, <90th percentile; PHT, ≥90th percentile and <95th percentile; HT, ≥95th percentile.

Figure 13: **Systolic and DBP percentiles and their distribution in the population.** showcases the relative density of systolic and DBP percentiles in all test subjects in a histogram. Skewness is 0.45 for SBP and 0.34 for DBP, respectively.

A scatter plot of systolic and DBP data of the whole population is displayed in

Figure 14: **Systolic and diastolic blood pressure data of the whole population.** It displays the relationship between SBP and DBP. Correlation is positive at 0.50 and significant.

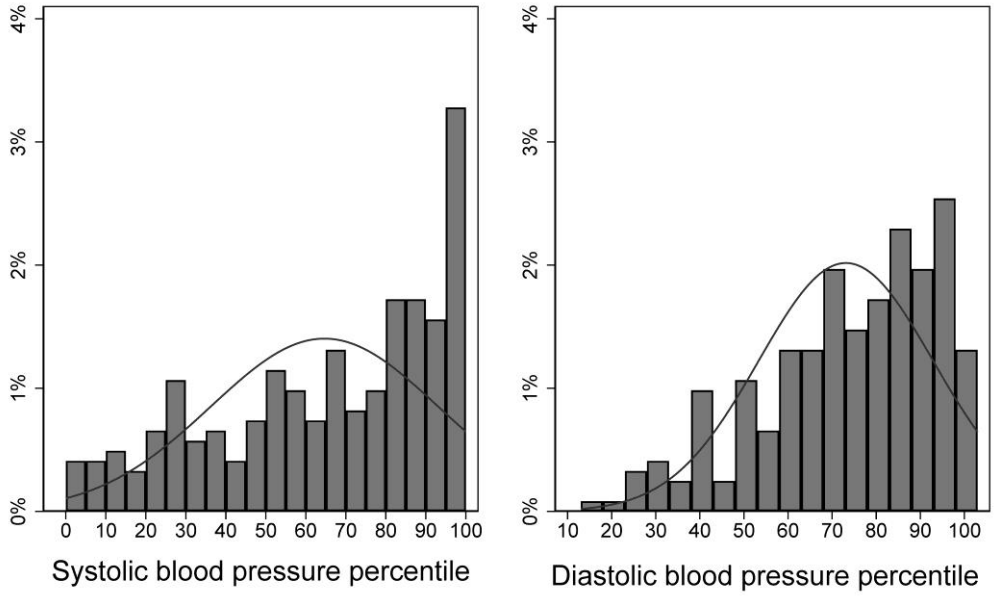

Figure 13: Systolic and DBP percentiles and their distribution in the population.

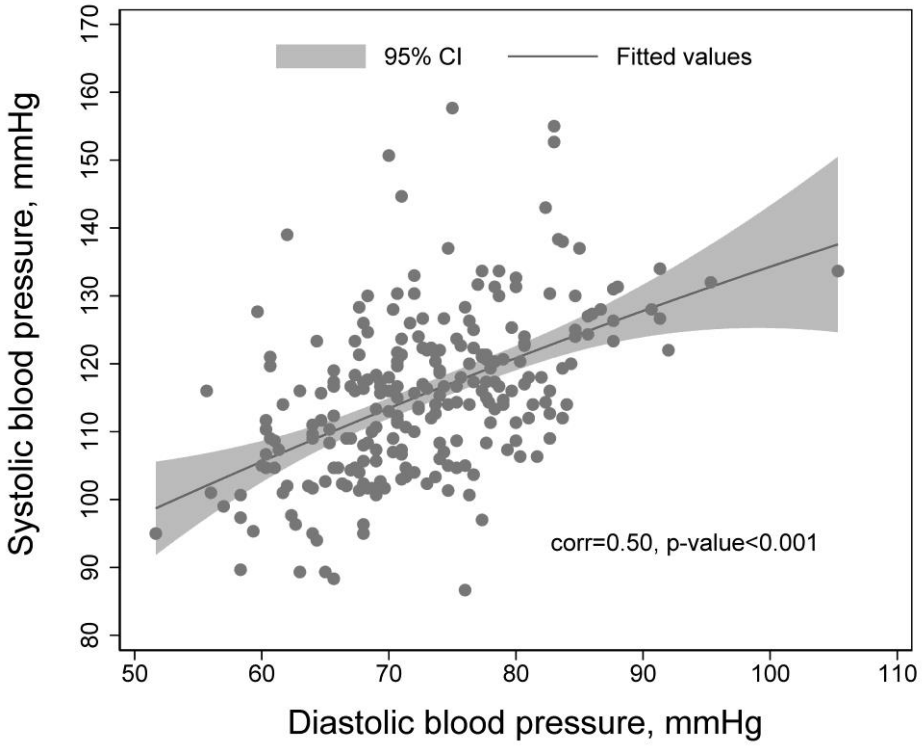

Figure 14: Systolic and diastolic blood pressure data of the whole population.

3.3 Exploration of clinical risk factors: subgroup analysis

Subgroup analysis was performed to investigate a putative association between sex and hypertension and between BMI and hypertension. For all further analysis, PHT and HT are combined and classified as elevated blood pressure. Differences in prevalence of hypertension were studied for specific subgroups. Prevalence of hypertension did not differ significantly according to sex of students 39,9% in females, 35.7% in males (Chi^2 p=0.679). (**Table 7**)

Scatter plots of systolic and DBP over BMI, respectively, are displayed in **Figure 15**. SBP and BMI have a positive correlation of 0.40 ($p < 0.001$). DBP and BMI have a weaker correlation of 0.18 ($p = 0.005$).

28,7% of lean (Underweight and Healthy weight) students had elevated blood pressure, while almost two thirds (61.0%) of overweight or obese adolescents had either pre-HT or HT. Detailed results of effects of BMI on blood pressure are displayed in **Table 8**. Probability of elevated blood pressure increased by 13% per unit increase of BMI (odds ratio: 1.13 [95% confidence interval: 1.06-1.19], p<0.001). This increase in risk prevailed in multivariable analysis adjusted for age and sex (multivariable odds ratio: 1.14 [95% CI: 1.07-1.21], p<0.001).

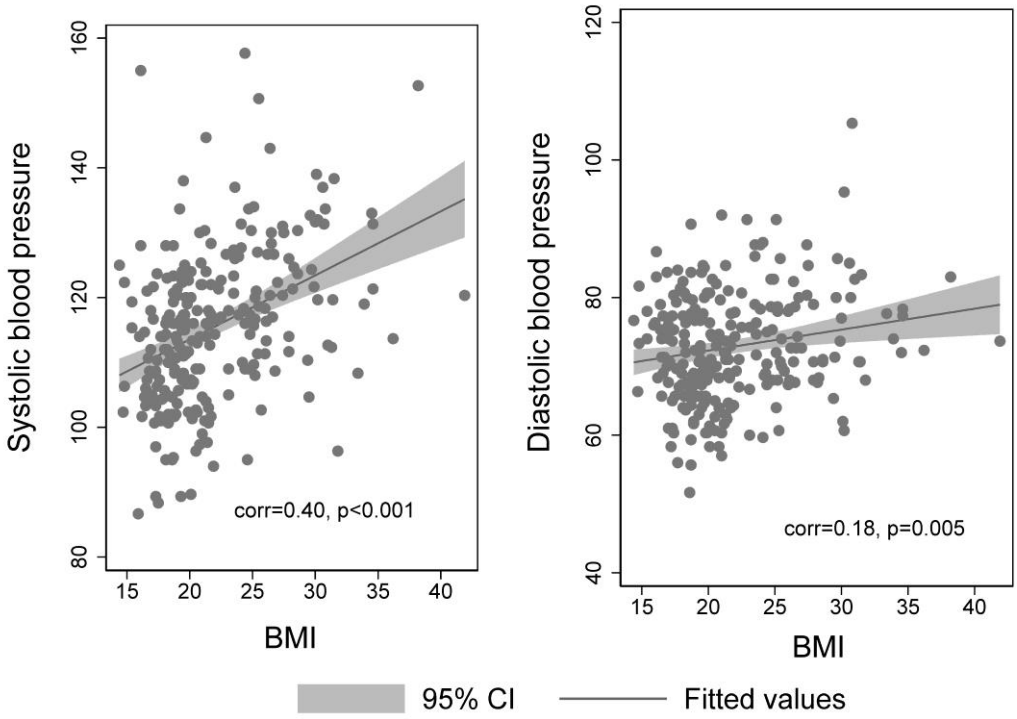

Figure 15: Scatter plots of systolic and diastolic blood pressure over BMI.

Table 7: Prevalence of elevated blood pressure in females and males.

	Normotensive	Elevated Blood pressure	Total
Female	113 (60.1%)	75 (39.9%)	188 (100%)
Male	36 (64.3%)	20 (35.7%)	56 (100%)
Total	149 (61.1%)	95 (38,9%)	244 (100%)

Table 8: Effects of BMI on blood pressure.

	Normotensive	Elevated blood pressure	Total
Underweight	7 (77.8%)	2 (22.2%)	9 (100%)
Healthy weight	112 (70.9%)	46 (29.11%)	158 (100%)
Overweight	19 (48%)	20 (51.3%)	39 (100%)
Obesity	11 (29.0%)	27 (71.0%)	38 (100%)
Total	149 (61.1%)	95 (38.9%)	244 (100%)

4 Discussion

This cross-sectional cohort study assessed the prevalence of pre-hypertension and hypertension and its relationship to obesity in adolescents living in Mthatha, South Africa. Since the adult population in the region of Mthatha is known to have a high prevalence in hypertension, there was reason to suspect a high prevalence in adolescents as well. The present study found pre-hypertension or hypertension in over a third of the examined high school students (38.9%). The prevalence of obesity too was found to be quite high (31.6%). In a subgroup analysis the prevalence of elevated blood pressure levels in overweight or obese adolescents was even higher (61.0%), although the prevalence in lean adolescents was likewise surprisingly high (28.7%). More than half of the participating adolescents had elevated blood pressure or were overweight/obese. This is reason for concern since both of these are risk factors for cardiovascular disease. (75)

There seems to be an above average prevalence of hypertension in adolescents in Mthatha. This is suggested by the positive skewness of 0.45 and 0.34 for SBP and DBP, respectively, as seen in **Figure 13.** We did not expect to find such high numbers in prevalence of hypertension in adolescents, even though this is in line with the projected upward trend in prevalence of hypertension by Din-Dzietham and colleagues. They examined prevalence of hypertension in children in the US and found a relative increase of 37% from 1988 to 1999. (76) A similar trend in prevalence of hypertension is evident in adults. (2)

Although the factors responsible for this rise in prevalence probably differ in children and adults, obesity is a decisive element in both groups. (77) (78) In the present study, higher blood pressure levels were observed in overweight/obese than in lean adolescents. Scatter plots of systolic and DBP over BMI displayed in **Figure 15** suggest a statistically significant association between those values, with a positive correlation of 0.40 ($p < 0.001$) between SBP and BMI. This further affirms the fact that overweight/obesity should be considered a high-risk factor and plays a crucial role in development of hypertension regardless of age. This confirms with the findings of the Framingham study that with increasing BMI mean blood pressure increases as well. (79) Although correlation of hypertension and BMI is significant, Landsberg et al. (2008) and other studies have found that other obesity indices, such as waist-to-height ratio and waist circumference are even more associated with hypertension. Therefore, waist-to-height ratio and waist

circumference could be better predictive factors to detect hypertension in daily clinical practice. (80) (81) Nevertheless, the current study showed that almost a third of all participants (31.6%) are obese. This is a more than threefold increase compared to the worldwide prevalence of obesity in adolescents of 10% conducted in 2013 by Pons et al. Other studies from South Africa looking at prevalence in obesity in adolescents report a prevalence of 13.5% to 25.5%. (82) Based on our results, it appears that the prevalence of overweight and obesity in South Africa is increasing. Our results in adolescents match the trend of a global increase in BMI values. (83) (84)

Mthatha, like many peri-urban communities in developing countries, has been undergoing a rapid transition and is modernising rather quickly. This results in a change in feeding habits and lifestyle. This could be a possible reason for increased obesity rates, which we did not measure in the present study. This is a limitation of our study, as some studies have shown that the time adolescents spent in front of a TV-screen or mobile phone screen has increased and could lead to obesity. For example Issartel et al. suggested a positive association between increased weight and the accumulated minutes of daily screen time engagement. (85) Another possible reason for high obesity rates in the adolescents that we measured in Mthatha could be related to the level of physical activity. However, we did not measure the level of physical activity in adolescents in Mthatha which could be another limitation of our study. For example studies have shown that reduced engagement in physical activity could be reason for an increase of obesity in adolescents. (86) Further studies investigating how adolescents spend their leisure time and how much they engage in physical activity are required. The results from such studies could be communicated to the public health authorities to help them design programs aimed at slowing down the current epidemic of obesity among adolescents and consequently reduce hypertension and cardiovascular risk in adulthood.

Furthermore, the high prevalence of pre-hypertension and hypertension in lean adolescents found in the present study (28.7%) causes serious concern. This affirms the belief that other factors should be considered a high-risk factor for development of hypertension during childhood. This is a limitation of our study, since we did not screen for any other risk factors but obesity. One possible risk factor could be family history of hypertension. A study conducted by Romo et al. (1999) found that hypertension develops in thin adolescents who have a family history of arterial hypertension. Romo et al. (1999) supports the view that some unknown type of renal defect might cause hypertension even in the

absence of obesity as a risk factor. Further studies investigating risk factors for hypertension in adolescents other than obesity are required.

Prevalence of pre-hypertension and hypertension found in the present study were remarkably high among adolescent boys and girls. In our study the prevalence did not vary significantly when stratified by sex, which was in line with findings of other studies. (69). The findings of this study suggest a higher vulnerability of children in Mthatha to CVDs, especially since raised blood pressure in children often persists into adulthood. (87) The correlation between hypertension and BMI could be a demonstration what the effects of a more sedentary lifestyle and over-feeding are on a population. Our results reinforce findings of other studies analysing the increase in prevalence of hypertension and pre-hypertension in other developing countries (88) (89), although the rate of increase seems to be higher in adolescents from South Africa.

5 Conclusions and future directions

Pre-hypertension and hypertension were found to be present in many adolescents in Mthatha, South Africa, at a prevalence of 38.9%. Elevated blood pressure levels were strongly associated with overweight and obesity. This high prevalence may put many of these children at risk for CVDs later in life. Therefore, intervention strategies are needed. School programs providing students with information about the interconnection of hypertension, obesity and CVD and its long-term effects may be useful to avert a potential rising incidence of CVDs.

Furthermore, additional studies determining the cause of hypertension in adolescents may be useful to halt further increase in prevalence of hypertension.

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