Genetics and the developmental origins of health and disease (DOHad); the effect of programming on childhood hypertension.

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1. Introduction

Hypertension is the chronic condition of elevated blood pressure. Blood pressure is the force against the walls of your vessels as the heart pumps around blood. There are two measures that characterize blood pressure. There is the measurement as your heart contracts, which is called systolic blood pressure. There is also the measurement as your heart is relaxed and filling with blood, this is called the diastolic blood pressure. Blood pressure is therefore described as systolic over diastolic in units of mmHg (written as systolic/diastolic, for example 120/80 mmHg).

Blood pressure is not constant during the day. Resting blood pressure, for example, is lower than the blood pressure during exercise. Blood pressure is considered normal when it is below 120/80 mmHg most of the time. Adults are diagnosed as having hypertension when their blood pressure is consistently above 140/90 mmHg. Adults with a blood pressure between 120/80 mmHg and 140/90 mmHg are considered pre-hypertensive and are at risk for developing hypertension.

Some medical conditions, such as chronic kidney disease, can cause hypertension. This is called secondary hypertension. When hypertension has developed without an underlying medical condition this is called primary or essential hypertension. In the Netherlands one in three people have hypertension. More men suffer from hypertension (37,4%) as compared to women (26,2%). The prevalence of hypertension also increases with age, the older you are the higher the likelihood that you will develop hypertension[1].

Primary hypertension can lead to other, dangerous, health problems. It can cause kidney problems, strokes and heart failure. Heart disease is the leading cause of death for men and women in the USA[2] and in Holland about a 140.000 people suffer from heart failure[3]. World-wide about 6 million people die because of a stroke every year[4]. It is therefore important to treat hypertension to prevent other medical conditions from developing and by these means prevent some of these deaths.

For a long time it was believed that hypertension in children only existed as secondary, caused by an underlying medical condition, and that it was a rare problem[5]. Sol Londe was one of the first to investigate childhood blood pressure. His research showed that blood pressure increased with age and growth[6]. Because of limited data on blood pressure in children it was unclear what could be considered normal. In the 70s the first charts describing normal blood pressure percentiles compiled from data collected from over 11,000 children were published by the National Heart, Lung and Blood Institute[7]. Since then more data has been collected and our understanding of childhood blood pressure has become more extensive. Childhood blood pressure charts now exists that give blood pressure as a function of age and height. The revised blood pressure table for children and adolescents was published in 2004 by the National Heart, Lung, and Blood Institute (NHLBI)[8]. Children are considered hypertensive when they have a blood pressure above 95th percentile for age, height and gender on three separate occasions. Children who have a blood pressure above the 90th percentile on three separate occasions are considered to be pre-hypertensive (for blood percentile charts see appendix 1 and 2).

With the availability of more data we have become increasingly aware of the existence of primary hypertension in children. The epidemiology of hypertension in children is not as well defined as in adults, but the prevalence has been reported as high as 5%[9]. Diagnosing childhood hypertension is not straightforward, because of several difficulties. The charts that are currently available are mostly comprised of white American children. Therefore they may not be indicative for other groups of children, such as children from Europe or ethnic minorities in the United States. Blood pressure can be measured in a variety of ways with different equipment, there is currently no standard measuring

technique. With the increased interest in childhood blood pressure these problems should be resolved in the future.

The clinical impact of childhood hypertension should not be underestimated, as it is thought to track from childhood to adulthood. This means that children with hypertension will become adults with hypertension[10]. Hypertension may also have short-term side effects on organ function, which are typically rare but can lead to life-threatening complications such as aortic dissection[11], intracranial haemorrhage, heart faillure[12] and encephalophaty[13].

It is important to understand the development of childhood hypertension because it has such a major impact on the patients' current and future health. Our future health is greatly impacted by genetics from our earliest development. We could call the functions of our genes programming. That genes play a role in our bodies' response is well known, but recently another form of programming has come to the fore. We now understand that around birth there is a time of plasticity that reacts to specific environmental factors and these reactions programme us for later life. I will describe how programming affects childhood blood pressure in two chapters; genetic risk factors and perinatal risk factors. This is important because these risk factors will indicate who are at risk and should be tested for hypertension. Furthermore, they constitute possible targets for prevention and treatment.

2. Genetic factors

In February 2001 the first maps of the human genome were published[29,30]. Since then continuing advances in DNA sequencing technology have made it possible to discover genes involved with diseases. Studies have shown that blood pressure is genetically regulated, with heritability estimates between 31% and 68%[31,32]. While there has been success in identifying genes that cause illnesses where one of the symptoms is hypertension, it has been much more difficult to find genes involved in primary hypertension. In this chapter both will be discussed, as well as evidence that genetics indeed play a role in childhood hypertension.

2.1 Monogenic Hypertension

With the recent advancements in DNA studies, most notably human genome mapping, some rare diseases have been traced back to a single mutation. Syndromes that are caused be a single gene, as opposed to multiple gene involvement, are called monogenic. In the case of hypertension most monogenic forms of hypertension are forms of secondary hypertension, i.e., hypertension that is caused by an underlying illness. Most monogenic forms of hypertension are caused by a gain-of-function mutation. These are mutations that cause new or improved activity of a protein. Gain-of-function mutations usually cause hypertension through an overproduction or increased activity of mineralocorticoids, these are a group of steroid hormones that affect our salt and water balances. Hypertension can also be caused in some of these syndromes through abnormalities of electrolyte transport, which is due to abnormal kidney function (For an overview of monogenic hypertension syndromes see Table 1).

Most of these genes were discovered through linkage analysis of large family groups, where a great number of individuals suffered from hypertension. This enabled researchers to find the region of the chromosome where the involved gene lies. This region was then screened for candidate genes to find the mutation that causes the disease[33].

Recently studies have been done in monogenic forms of hypertension, namely pseudohypoaldosteronism type 2 (PHAII) and primary aldosteronism, using exome sequencing. The exome is simply the protein coding part of the DNA. It only amounts to about 1% of the genome, but is estimated to contain about 85% of the disease causing mutations[34]. The advantages of this technique are that it is quicker and more exomes can be sequenced then whole genomes. Also mutations found in protein coding regions are easier to interpret than mutations found in non-coding regions. Therefore the information found in these studies have a more imidiate impact on our understanding of hypertension.

PHAII is a form of hypertension associated with elevated levels of potassium, low blood pH and increased salt reabsorption. In PHAII the genes *WNK1* and *WNK4* were identified to be involved using traditional linkage techniques[35]. Mutations in these genes cause reduced potassium excretion. However these mutations were not found in all families affected, therefore it was hypothesized that other mutations played a role in these families. 52 families were studied, 7 of which had mutations in the *WNK* genes, using exome sequencing. Two further genes were identified, Kelch-like 3 (*KLHL3*) and Cullin 3 (*CUL3*), that were responsible for PHAII in 41 of the families[36]. The transmission patterns differ for these mutations, they are dominant for the *WNK* genes and *CUL3*. *KLHL3* mutations however, have both dominant- and recessive transmission patterns. People with recessive mutations have an earlier onset of the diseases and the disease is more severe[36,37]. *KLHL3* and *CUL3* both encode for proteins involved in the ion-homeostasis regulation pathway[37].

In primary aldosteronism the affected individuals suffer from excessive aldosterone production. Primary aldosteronism is most often caused by bilateral hyperplasia, where both adrenal glands are hyperactive, followed by adrenal adenomas. A small number of somatic mutations were found in these tumors, using exome sequencing. The most frequent of these mutations was *KCNJ*5, it was hypothesized that mutations in this gene were responsible for monogenic forms of primary aldosteronism[38]. This was shown to indeed be the case in a family with severe hypertension[39].

Table 1

Forms of monogenic hypertension

Disorders	Symptoms	Genetics
Steroidogenic enzyme defects		
Steroid 11β-hydroxylase deficiency	androgen excess, masculinization of female infants and precocious puberty in male children. Two thirds of patients have hypertension, associated with mineralocorticoid excess, hypokalaemia, and metabolic alkalosis.	CYP11B1 mutation (encodes cytochrome P_{450}11β/18 of ZF); impairs the synthesis of cortisol and ZF 17-deoxysteriods
Steroid 11α-hydroxylase/17,20-lyase deficiency	Decreased cortisol and sex steroids. Affected persons present as female irrespective of genetic sex and fail to enter puberty. Hypertension due to corticosterone overproduction.	CYP17 mutation (encodes cytochrome P_{450}C17) impairs cortisol and sex steroid production
Hyperaldosteronism		
Primary aldosteronism	Overproduction aldosterone, causes potassium excretion and sodium retention. Sodium retention causes blood volume increase through water retention. Leads to hypertension.	Unknown; very rare in children; female/male ratio is 2.5-3/1
Adrenocortical hyperplasia	Underproduction cortisol and mineralocorticoids. Overproduction androgens. Abnormal growth and development. Early salt losing crisis (third week of life) can lead to hypertension in later life.	Unknown. Monogenic inheratance pattern, gene not yet identified.
Idiopathic primary aldosteronism	Overproduction aldosterone, causes potassium excretion and sodium retention. Sodium retention causes blood volume increase through water retention. Leads to hypertension.	Unknown. As above
Glucocorticoid-remediable aldosteronism (GRA) Familial hyperaldosteronism type 1	Supressed renin secretion. Overproduction aldosterone, causes potassium excretion and sodium retention. Sodium retention causes blood volume increase through water retention. Leads to hypertension.	Chimeric gene that is expressed at high level in ZF (regulated like *CYP11B1*) and has 18-oxidase activity (CYP11B2 functionality)
Familial hyperaldosteronism type 2	Overproduction of aldosterone due to increased cell proliferation of the adrenal cortex and/or an adenoma producing aldosterone.	Unknown. A 5-MB locus on chromosome 7p22 appears implicated
Apparent mineralocorticoid excess (AME)	Elevated levels of cortisol in kidney, increased aldosterone-like effect, causes hypokalaemia, hypernatremia and hypertension.	Type 2 11β-OHSD mutations
Mineralocorticoid receptor gain-of-function	Low-renin, low-aldosterone, hypokalaemia and hypertension due to a change in the binding	Missense mutation – serine at amino acid 810 in the mineralocorticoid receptor is

mutation	region of the mineralocorticoid receptor.	changed to leucine (S810L)
Nonsteroidal defects		
Liddle's syndrome	Dysregulation of sodium channel which leads to increased sodium absorption. Leads to hypertension due to increased water retention.	Autosomal dominant abnormality, genetic mutation at the 16p13-p12 locus. SCNN1B or SCNN1G. Change or deletion PY motif.
Pseudohypoaldosteronism II—Gordon'syndrome	Inhibition Na-Cl transporter, reduced potassium excretion, up regulation co-transporters. Increased chloride and sodium reabsorption. Causes impaired growth, intellectual impairment, dental abnormalities, muscle weakness and severe hypertension.	Autosomal dominant Abnormality in WNK1, WNK4, CUL3. Dominant and recessive mutations in KLHL3
Brachydactyly and hypertension	Growth defect, shortened toe and finger bones, and hypertension.	Inversion, deletion, and reinsertion at 12p12.2 to p11.2

As adapted from Ingelfinger J.R. [14]

2.2 Hypertension related to cancers

Some cancers can also be seen as a monogenic form of hypertension. These cancers are caused by a germ line mutation, a mutation in a reproductive cell, that lead to pheochromocytoma. Pheochromocytoma are tumours formed from adrenal tissue which excrete hormones. They mostly excrete norepinephrine and to a lesser extent epinephrine. Norepinephrine raises the blood pressure, by vasoconstriction, and as such these tumours cause hypertension (Table 2).

Table 2

Hereditary syndromes associated with pheochromycytoma

Syndrome	Symptoms	Risk of pheochromocytoma	Mutated Germ-Line Gene
MEN-2A	Carcinoma (cancer that begins in the skin or lining of organs) of the thyroid, adrenal glands, *parathyroid glands*. Occasionally abnormal protein deposits on the skin occur. Symptoms depend on depend on the glands affected.	50%	*RET* (proto-oncogene)
MEN-2B	Tumors of the mouth, eyes and submucosa of almost all organs.	50%	*RET* (proto-oncogene)
Neurofibromatosis type 1	Neurofibromas, benign tumors of the peripheral nervous system, café au lait spots	1%	*NFI*
Von Hippel-Lindau disease (retinal cerebellar hemangioblastosis)	Blood vessel tumors of the eye, brain and spinal cord	10-20%	*VHL*
Familial paraganglioma syndrome	Tumors of the endocrine- and nervous system	20% (estimated)	*SDHS*, *SDHB*

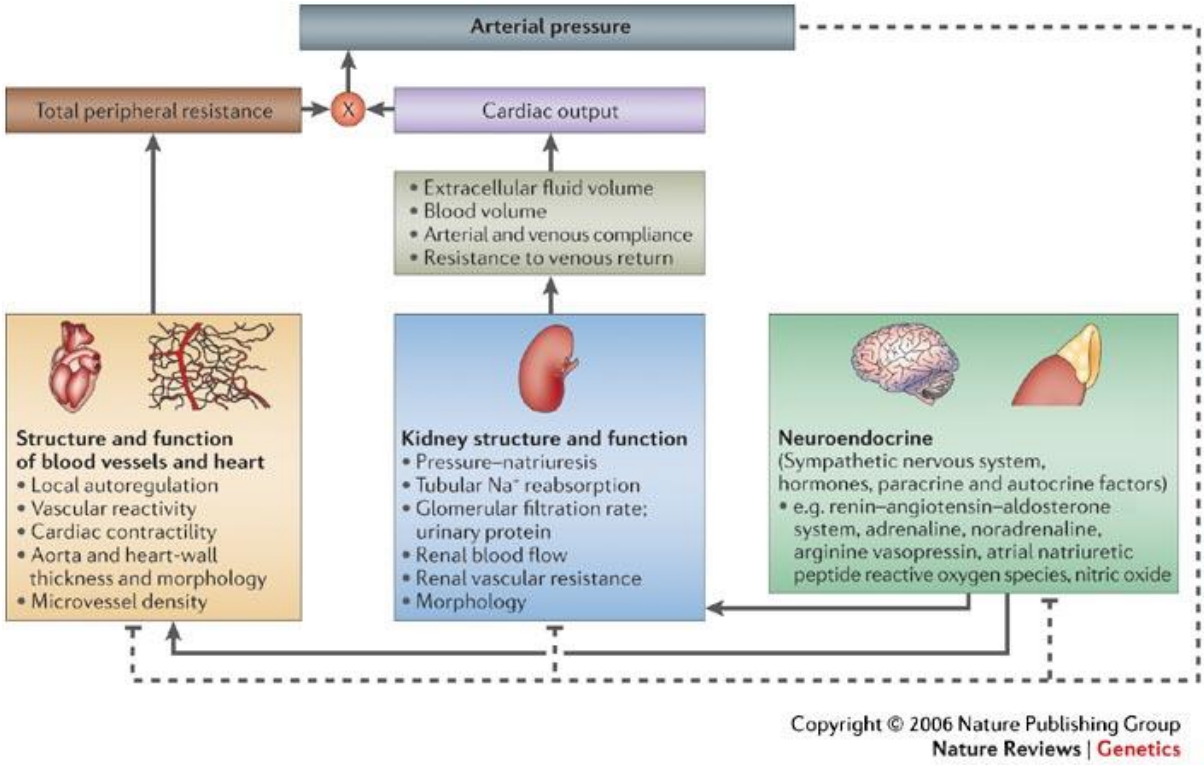
As adapted from Ingelfinger J.R. [14]

2.3 Polygenic Hypertension

Hypertension is a chronic condition which is widely prevalent in the population. Conditions that affect many people are often thought to be caused by multiple genes, they are polygenic. In polygenic conditions, and polygenic hypertension especially, it is very difficult to find the actual genes involved. This is because of a number of factors. In polygenic hypertension a single gene has a

small impact on the blood pressure. This is in part because blood pressure is a continuous variable and also because these genes interact with each other and the environment to cause hypertension. Another factor is that these genes are also present in people who are normotensive, because the specific gene-gene or gene-environment interaction to cause hypertension might not be present. Also the blood pressure regulatory system is fairly complex. It is the product of cardiac output and vascular resistance. These are both influenced by a variety of factors, including ion-homeostasis and the neuro-endocrine system (see picture 1). Because of this many genes can have a possible impact on blood pressure. Therefore, until the advent of genome-wide association studies (GWAS) it has proven difficult to find specific genes or genetic regions of interest for hypertension[14].

Picture 1. Mechanism of arterial blood pressure regulation



Cowley AW.[40] Arterial blood pressure is the product of total peripheral resistance and cardiac output. Cardiac output is affected by extracellular fluid volume, blood volume, resistance to venous return, arterial and venous compliance as well as kidney structure and function and the neuroendocrine system. Total peripheral resistance is affected by the structure and function of blood vessels and heart. It is also affected by the neuroendocrine system. Arterial pressure, total peripheral resistance and cardiac output are also all affected by homeostatic negative feedback (dotted line).

Despite these difficulties some tentative links were made. Several animal models have been used to study hypertension. Early inbred rat strain studies found candidate regions on nearly all chromosomes, however these studies were not able to identify any genes or their associated alleles[41,42]. Targeted deletion studies in mice have found over a dozen genes involved in blood pressure, including insulin receptor substrate, endothelial nitric oxide synthase, the dopamine receptor, the angiotensin type 2 receptor and other parts of the renin-angiotensin system[43]. Focussing on the renin-angiotensin system, many genetic manipulation studies were done. These

include inbred rat strain models. These models point to the gene coding for angiotensin-converting enzyme (ACE) as being important in determining hypertension[15,16]. Following this there have been several studies that point to a link between human hypertension and genes of the renin – angiotensin system as well[17,18].

Animal models may not be the best way the discover which genes could possibly pay a role in human hypertension. Though blood pressure regulation may be similar on many levels there are of course differences. In such a complex system genes may be found in animal models that play no role in human hypertension, and genes that are important in human hypertension may not be found in animal models. Also many of the models that are used rely on inbred strains. It is possible that these inbred strains develop pathogenesis of their own that are not reflective of the pathogenesis of primary hypertension in a normal population. Therefore to study the genetics of human hypertension it is important to also do DNA studies in humans.

2.4 Familial aggregation

The research done in identifying genes involved in polygenic hypertension has proven difficult. However studies have been done that prove genetics indeed play a role in hypertension, and even play a role in childhood hypertension.

In the 1960s a number of large family studies showed that blood pressure was similar among first degree relatives[24,25]. This similarity in first degrees relatives is called familial aggregation. Later studies looked whether familial aggregation also held for children. They looked at the correlation between siblings and the correlation between children and their mother. In both cases familial aggregation was shown[26,27]. These studies did leave a number of questions, not the least of which is whether this familial aggregation is caused by shared environmental factors or shared genetics.

To investigate whether genes or environment were the most important factors in familial aggregation in children a number of twin studies were done. In these studies monozygotic twins are compared to dizygotic twins. Monozygotic twins share a 100% of their DNA as opposed to dizygotic twins who on average share about 50% of their segregating DNA. Therefore if genetics play a role in blood pressure there should be a higher level of similarity in blood pressure of monozygotic twins then dizygotic twins. In a variety of these studies it was found that familial aggregation of BP is caused in a large part by genetic influences[28].

2.5 GWAS

Knowing that genetics play a large part in blood pressure regulation, studies keep being done to find the genes involved. Where linkage methods have proved unsuccessful for elucidating polygenic hypertension, GWAS studies have had more success. GWAS researches the association between common genetic variations in a population and a selected trait, such as hypertension. These common genetic variations are usually single nucleotide polymorphisms (SNPSs). A SNP is a genetic variation occurring in a single nucleotide of the DNA sequence within a population. Across the whole of the genome many of such SNPs occur. With the sequencing of the human genome and several projects to find these SNPs, such as the HapMap project[19], many of these SNPs are now known. The association of SNPs to hypertension points to specific regions of the genome, where candidate genes can be found.

Even using GWAs it is difficult to find genes involved in blood pressure and hypertension. Combining several studies into the GlobalBPgen and the CHARGE consortia proved successful and 13 novel blood pressure loci were identified[20,21]. These were the first successful GWAS studies and showed that loci involved in blood pressure could be identified using large sample sizes. Since then a number

of other studies have also been able to identify loci of interest. The studies done by the International Consortium for Blood Pressure Genome-Wide Association Studies (ICBP) and by Tragante, *et al.* give the most complete overview of loci currently known to be associated with blood pressure, they show 40 loci in total[44,45] (see table 3).

Table 3. Loci associated with blood pressure

Locus	SNP	Chromosome	Effect Allele
Tragante et al.			
PDE1A	rs16823124	2	A
HLA-DQB1	rs2854275	6	A
VCL	rs4746172	10	C
H19	rs217727	11	A
NUCB2	rs757081	11	G
RELA	rs3741378	11	T
CDK6	rs2282978	7	C
FBN1	rs1036477	15	G
NFAT5	rs33063	16	A
PRKAG2	rs10224002	7	G
HOXC@	rs7297416	12	C
ICBP			
MOV10	rs2932538	1	G
SLC4A7	rs13082711	3	T
MECOM	rs419076	3	T
SLC39A8	rs13107325	4	T
GUCY1A3-GUCY1B3	rs13139571	4	C
NPR3-C5orf23	rs1173771	5	G
EBF1	rs11953630	5	T
HFE	rs1799945	6	G
BAT2-BAT5	rs805303	6	G
CACNB2(5')	rs4373814	10	G
PLCE1	rs932764	10	G
ADM	rs7129220	11	G
FLJ32810-TMEM133	rs633185	11	G
FURIN-FES	rs2521501	15	T
GOSR2	rs17608766	17	T
JAG1	rs1327235	20	G
GNAS-EDN3	rs6015450	20	G
MTHFR-NPPB	rs17367504	1	G
ULK4	rs3774372	3	T
FGF5	rs1458038	4	T
CACNB2(3')	rs1813353	10	T
C10orf107	rs4590817	10	G
CYP17A1-NT5C2	rs11191548	10	T
PLEKHA7	rs381815	11	T
ATP2B1	rs17249754	12	G
SH2B3	rs3184504	12	T
TBX5-TBX3	rs10850411	12	T
CYP1A1-ULK3	rs1378942	15	C
ZNF652	rs12940887	17	T

Tragante, et al.[44] and ICBP[45]

Loci involved in blood pressure can also be found using extreme case-control designs. A study done in a Swedish population looked at the top 2% and bottom 20% of the blood pressure distribution. This study pointed to a gene, the Uromodulin gene, which is only expressed in the kidney. It is possible that a mutation here affects the sodium homeostasis and can thus predispose a person towards hypertension[22].

GWAS studies should also take different ethnic groups into account. A large scale GWAS study done in East-Asians showed that they differed from previously investigated European populations. While 7 loci were found that were initially identified in European population, 6 novel loci were also discovered. Interestingly one locus, ALDH2, showed strong association to systolic- and diastolic blood pressure mostly mediated by alcohol intake[46]. Investigating different ethnic groups also throws up new difficulties. Two initial GWAS studies in African-Americans did not find any loci that reached genome wide significance[47,48]. African-Americans are an ethnic group where different ancestral groups (European, Africans) recently mixed. It was shown by Zhu, *et al.* that in such population it is better to first do admixture mapping, a method of gene mapping that makes use of the fact that a population has recently become mixed, and then follow-up association analysis. In this way they were able to identify a novel variant[49].

GWAS studies are limited in that they point towards certain regions as being involved in hypertension, but do not tell us how changes in these regions can potentially lead to hypertension. To understand the mechanism that leads to hypertension the data from GWAS studies must be followed up using so called post-GWAS analysis. First candidate genes must be found in the loci of interest, this can be done using bioinformatics. After this in vitro and in vivo studies must be done to discover a potential disease mechanism[23].

So far the GWAS studies that have been done have not looked at the involvement of SNPs in childhood hypertension. To find genes involved in childhood hypertension further research is required.

3. Perinatal Factors

3.1 DOHaD

During early development, the time around birth, there is a phase of developmental plasticity. This developmental plasticity is a tool that prepares us for the environment in which we are born. However if the period around birth is not actually representative of the conditions we experience in later life it can be detrimental to our health and set us up to develop certain chronic conditions. This phenomenon is described in the Developmental Origins of Health and Disease (DOHaD) hypothesis. According to this concept certain factors around birth, perinatal factors, could impact on childhood blood pressure and blood pressure later in life.

3.2 Birth weight

Birth weight is a factor that has been reported to have an effect on childhood blood pressure. There are a number of studies that show that a low birth weight is inversely correlated to blood pressure. Children with a low birth weight have higher blood pressure as compared to children with a normal birth weigth[50-52,86-88] . Low birth weight for full term infants is below 2,500 g[85]. Though most studies looked at children that were full term, some of these studies did not. In these cases low birth weight was defined as children that were small for gestational age[59]. In some of the studies that found low birth weight associated with high blood pressure, this effect was stronger after correction for current weight[86-88].

Not all studies agree on the effect of birth weight on blood pressure. There are a number of studies that have found that post-natal weight gain has much larger influence on childhood blood pressure[53,54,55]. Increased weight gain is associated with an increase in blood pressure. Studies do not agree at which time weight gain has the greatest influences on blood pressure. It has been found to mostly influence blood pressure during the first six months[55], but other studies have reported that the effect was greatest after six months of age with the most recent weight changes being the most important[53].

It is also argued that in studies linking birth weight to blood pressure certain factors, such as genetic factors or low socioeconomic factors, have not been taken into account[56]. When a factor that has not been taken into account affects the correlation between two variables this is called collider-stratification bias. A sensitivity analysis was done to discover whether the inverse correlation between birth weight and blood pressure could be explained by collider-stratification bias. It was concluded that the inverse correlation could not be explained by collider-stratification bias alone[57].

Blood pressure varies during development and is greatly influenced by height. In the assessment of high blood pressure in children blood pressure percentiles that are height adjusted are now widely used[58]. Looking at the blood pressure percentile as opposed to absolute blood pressure might give a clearer picture of the effect of birth weight. Birth weight is not a reliable predictor for later stature. Children with similar birth weight can vary greatly in height at the time of measurement, as well as the height they reach in adulthood. Therefore the use of height adjusted percentiles will minimize the confounding effect of height. In a population based, cross-sectional study of 887 Icelandic schoolchildren aged 9- to 10 years old, it was found that birth weight was correlated to blood pressure percentile and not to absolute blood pressure values. A decrease in birth weight from 4500 to 2500 g was found to be predictive of a rise in systolic blood pressure of 8.5 percentiles[59]. Two other studies have also reported an inverse correlation between birth weight and standardized

blood pressure[89,90]. Blood percentiles should be examined more thoroughly in future to give a clearer picture (for overview blood percentile charts see appendix 1 and 2).

The association between birth weight and blood pressure does not appear to be linear. A number of studies have reported that increased birth weight put children at risk for developing elevated blood pressure. In a studied of Chinese children aged 3 to 6 years the association between elevated blood pressure and birth weight and postnatal weight gain was investigated. Elevated blood pressure was defined as blood pressure above the 90th percentile for age and gender. Greater birth weight was found to be associated with an increased risk for elevated blood pressure. This risk was found to be even more increased when greater birth weight was combined with greater postnatal weight gain[91]. Another study that looked at birth weight and blood pressure in 7 year old children from the US also reported an increased birth weight to be associated with the risk for elevated blood pressure. Interestingly when the effect was adjusted for race it was found that this positive association persisted for black children, but no association was found for white children[92].

There are several hypotheses as to how birth weight affects blood pressure. One of these is the thrifty phenotype, where low birth weight is thought to influence hypertension through a mechanism which causes the foetus to be programmed towards a thrifty phenotype[60,61]. Children have a lower birth weight because of malnutrition during gestation. This impacts the developmental plasticity discussed earlier and causes the child to be programmed to take advantage of limited nutritional and environmental resources. When the resources are not limited such a phenotype puts a child at risk toward developing hypertension as well as other health problems[93]. It is also possible that children with a low birth weight have an increased risk of hypertension, because of vascular dysfunction. Which is caused by growth restriction during foetal development[94-95]. Also a combination of low birth weight and post-natal weight gain can cause a child to have an increased risk for developing hypertension[53]. Finally the effect of post-natal weight gain and a high birth weight could indicate that excessive foetal growth and over nutrition have an impact on later health. This could be caused by permanent changes in metabolism and appite[98].

3.3 Poor maternal diet

In human malnutrition it is difficult to quantify which resources are specifically deficient and the amount of deficiency. Nevertheless studies have been done which look at different resource deficiencies and the effect on hypertension. To look at protein-calorie malnutrition researchers examined the children of women pregnant during the Dutch famine. The average calorie intake of these women was below 900 kcal/day for several months. It was found that offspring who were exposed to malnutrition during the second trimester had an increased risk for developing hypertension. Those who were exposed during the first and third trimester had other increased risks, including raised lipids, altered clotting and decreased glucose tolerance[62,63]. Therefore protein/calorie malnutrition is a risk for high blood pressure at a certain time during gestation, probably caused by foetal programming being time specific.

Vitamin A deficiency as associated with renal abnormalities, and as such could increase the risk for hypertension[99]. It has been shown that even a mild vitamin A deficit can lead to changes in the kidney in rats[100]. It is difficult to research the effect of vitamin A deficiency in humans. However a study that compared children from Bangalore (in India) with children from Montreal (in the US) found that the kidneys of children from Bangalore were smaller at birth. It was also observed that the vitamin A levels in mothers from India was lower as compared to mothers from the US[101].

A high salt diet is a well-known risk factor for hypertension and can already affect blood pressure during childhood[102]. Maternal high salt intake is also a risk factor for hypertension, in that it can

cause changes in the renal structure[103,104]. Rats receiving a high salt diet during the perinatal period were found to have hypertension associated with increased sympathetic nervous activity, which was caused by increased activity of the Angiotensin II receptor, type 1 (AT_1 receptor). Activation of the AT_1 receptor leads to vasoconstriction and aldosterone secretion. Data concerning high perinatal salt intake in humans is limited. However children with a low birth weight are reported to be more sensitive to salt and have an increased elevation in blood pressure in response to a high salt diet[105].

3.4 Placental Vascular Dysfunction

As discussed foetal malnutrition is a risk factor for childhood hypertension. This foetal malnutrition does not necessarily have to be caused by a poor maternal diet, it can also be caused by dysfunctions in the placenta. The foetus is connected to its mother's bloodstream through the placenta. This functions as a barrier that protects the foetus, while being able to pass on vital nutrients and oxygen as well as take up waste. Therefore a placenta that does not function properly can cause foetal malnutrition, which in turn can lead to problems in cardiovascular function in later life[64-66]. Placental vascular function can be assessed using ultrasound. Two measures can be derived from this: feto-placental- and utero-placental vascular resistance. Increased vascular resistance indicates a problem in the placental vascular development.

The Generation R Study looked at placental vascular dysfunction and its effect on cardiovascular development, including blood pressure. They did a population analysis on 6716 mothers and their children, the blood pressure measurements were done when the children were 6 years of age . They found that in children with impaired placental vascular function systolic blood pressure was higher. This association was even stronger among girls and could not be explained by birth weight[67]. This indicates that placental vascular dysfunction is indeed a risk factor for the development of childhood hypertension.

3.5 Preterm delivery

In humans gestation is complete at 37 weeks, when a baby is born before this it is called preterm birth. Preterm birth can cause a number of health problems, because babies are born before organ systems are properly developed. The earlier the baby is born the higher the likelihood of neonatal morbidity and mortality. Preterm birth can affect a number of organ systems, including kidney development. Preterm babies are often observed to have renal problems and the incidence of renal failure of children admitted to the intensive care ranges from between 8% to 24%[106-109]. The kidney greatly influence blood pressure, therefore preterm birth is likely to also affect blood pressure. There is increasing evidence that links pre-term birth to adult hypertension[68-70].

Research has shown that late-preterm birth is a risk factor for childhood hypertension. Late preterm infants are born between the 34th and 37th week of gestation. Kidney development, nephrogenesis, last until the 36th week of gestation[71]. It is therefore likely that these late-preterm infants have a nephron deficit at birth. Researchers looked at the blood pressure of 65 late-preterm children aged 4 to 13 years old using ambulatory monitoring, and compared this with 65 age and sex matched full-term children. Both daytime and night-time blood pressure were found to be significantly higher in late-preterm children[72].

Late-preterm children have a higher risk, than children that are full-term, for developing hypertension. A recommendation could be made for monitoring these children's blood pressure. This way problems can be caught early and these children can be treated in a timely manner.

3.6 Maternal obesity

Children born to obese mothers have a greater chance to have an adverse cardiovascular risk profile in childhood and adulthood[73,74]. Children were considered to have an adverse cardiovascular risk profile when 3 or more of the following factors were found: android fat mass% above the 75th percentile (android fat is a greater deposition of central fat, i.e. fat around the gut); systolic or diastolic blood pressure above the 75th percentile; high-density lipoprotein cholesterol below the 25th percentile or triglycerides above the 75th percentile; and insulin levels above the 75th percentile[76].

This increased risk for an adverse cardiovascular risk profile could be caused by the foetus being exposed to an increased amount of nutrients while in the womb. This could lead to permanent adaptations in its metabolism, appetite and neuroendocrine function[75]. These alterations occur through interaction of extracellular signalling factors, intracellular transcription responses and nutrient-induced epigenetic alterations, the maternal environment can thereby program the foetus[110]. These mechanisms are not yet fully elucidated and need to be further researched.

Maternal obesity could impact hypertension through foetal programming. However, obesity is a well-known cardiovascular risk factor. The greater chance of an adverse cardiovascular risk profile can also be a consequence of the child's greater risk for developing obesity through a shared family environment or a shared genetic profile.

The Generation R study looked at both maternal and paternal BMI as related to an adverse childhood cardiovascular risk profile, which included blood pressure measurements. This way a distinction could be made between foetal programming and a shared family environment and genetic profile. If the increased risk is caused by a shared family environment and genetic profile you expect the association to be similar for both parents BMI. They found that systolic- but not diastolic blood pressure in children was associated with both a higher maternal BMI and higher paternal BMI, but the association was stronger for maternal BMI than paternal BMI. The association between parental BMI could mostly be explained by the children's own BMI. When corrected for the children's own BMI there was still a small positive association between maternal BMI and systolic blood pressure[76].

Maternal obesity is a risk factor for childhood hypertension. However it seems mostly to be a result from childhood obesity[76]. Foetal programming does appear to play a role, and has also been reported to play a role in the development of obesity[110]. However family environment and genetic predisposition cannot be excluded. Though it is probably especially difficult for these children, because of foetal programming and/or genetic predisposition, hypertension in these cases could be prevented by implementing a healthy diet and thus preventing obesity.

3.7 Parental Smoking

The exposure of the foetus to adverse environmental factors may lead to foetal adaption that has a detrimental effect on cardiovascular development. Parental smoking is a very common, devastating and easily preventable adverse environmental factor that a foetus can be exposed to. It is well documented that parental smoking can lead to preterm-birth and a low birth weight[77,78]. Researchers have also found that parental smoking has an effect on the cardiovascular development and that there is an association between maternal smoking and a higher childhood blood pressure[79-82]. It is not clear whether this effect is caused by direct intrauterine mechanisms, e.g. placental dysfunction or other unknown confounders.

To get a clearer picture whether or not smoking causes differences in intrauterine mechanisms it is possible to compare the effects of maternal smoking as opposed to paternal smoking. If high blood pressure has a higher association to maternal smoking it is likely that this is associated with an intrauterine mechanism causing cardiovascular problems. The Generation R study compared the level of association between blood pressure of 6 year old children and maternal and paternal smoking. It was found that both were associated with a higher diastolic blood pressure, but maternal smoking was much more strongly associated. Furthermore this association appeared to be dose dependent[83]. The fact that maternal smoking is more strongly associated probably means that there is indeed an underlying intrauterine adaptive mechanism. However the possible mechanisms behind this are not yet clear.

Parental smoking puts children at risk for hypertension as well as a host of other health problems such as asthma. It is therefore to be advised that pregnant women should not smoke and their partners should not expose them to smoke. This will protect the unborn child and prevents possible future health problems. Researching the mechanism behind which smoking could affect childhood hypertension could lead to other preventive measures. This might help those children whose parents are not able to stop smoking.

3.8 Timing and prevention

The adaptations that a foetus undergoes because of adverse environmental conditions may occur during a specific part of the pregnancy. Foetal adaptations that take place during the first trimester have been linked to a cardiovascular risk profile, which includes a higher blood pressure[84]. Children that are exposed to certain risk factors during the first trimester, such as smoking, should be monitored. When the development of high blood pressure is caught early, treatment can be undertaken which will prevent further health problems later in life.

4.Discussion

One in three people suffer from hypertension in the Netherlands[1]. This is a major risk for public health because hypertension can lead to other health problems, such as strokes and heart failure. Hypertension can develop during childhood and is thought to track to adulthood[10]. It is therefore important to understand what the risk factors are for developing childhood hypertension, as it has a great impact on current and future health.

4.1The importance of future research into genetics

There have been a number of studies that have shown blood pressure is, at least in part, genetically regulated. Heritability is estimated between 31% and 68%[31,32] and familial aggregation has been found to be mostly mediated by genetics[28]. Our current knowledge of genetics can only explain a fraction of this heritability however, so much is still to be done.

Most success has been had in identifying genes for monogenic forms of hypertension. This has been important in understanding the mechanism that cause hypertension in these cases. Children who suffer from these forms of hypertension can be diagnosed and given a specific treatment. Not for all forms of monogenic hypertension have the genes involved been found. Also for some forms our knowledge of the genes involved is still incomplete, it is likely that many novel variants exist[33]. It is important to discover these variants to identify new pathways for pharmaceutical intervention. Monogenic forms of hypertension could be further investigated using exome sequencing. Exome sequencing has several advantages as compared to whole genome sequencing. Data from more people can be collected faster and cheaper. Most of our current knowledge of monogenic hypertension comes from linkage studies[33]. GWAS studies could also be done on large numbers of cases of monogenic hypertension to find new genes involved.

Polygenic hypertension was first researched in animal studies and some tentative links were made, mostly involving the renin-angiotensin system[17,18]. However the usefulness of animal models could be questioned. Though the animal models might be comparable to human, differences will always exist and are probably greater in such complex systems as blood pressure regulation. Also many of the animal models were based on inbred strains. It is quite possible that these inbred strains developed pathogenesis that is not representative for normal populations.

GWAS studies have proven to be a breakthrough in identifying genes involved in polygenic hypertension. The studies done by the International Consortium for Blood Pressure Genome-Wide Association Studies (ICBP) and by Tragante, *et al.* have identified 40 loci involved in blood pressure regulation[44,45]. Much work is still to be done though, as DNA sequencing techniques improve more studies have to be done to identify other possible loci involved. It is important when identifying loci involved in blood pressure regulation to also look at different ethnic groups. Since novel loci have already been found in African American and East Asians as compared to European populations[46,49]. It is also important to look at the difference between genders, because men have a higher risk for developing hypertension it is possible that different genes are involved. Finally researchers have only looked at genetics in adults. It is important for future research to find the genes that influence blood pressure in early childhood. Understanding how genes affect the blood pressure early in life is an important step in finding new ways of treating and preventing hypertension. If we can effectively lower blood pressure at an early age we can stop hypertensive children from becoming hypertensive adults.

4.2 The importance of future research into perinatal factors

The DOHad hypothesis states that certain factors around our birth impact on later health. This is caused by a phase of developmental plasticity around the time of our birth. This phase probably arose during evolution, because children adapted to the environment they were born in had a better survival rate.

One of the factors described to have an impact on hypertension is birth weight. Though not all studies agree how and if birth weight impacts hypertension. Low birth weight is reported to be associated with hypertension, some studies also report high birth weight to be associated with hypertension. Post-natal weight gain is reported in some studies to be more strongly associated then birth weight itself[98]. Studies might show conflicting results, because not all confounding factors have been taken into account. Also not all studies correct for confounding factors, such as current weight, in the same way. Another important factor is age, birth weight could have different influences on hypertension at different ages. To get a clearer picture of the actual effect of birth weight on hypertension future studies should have more uniformity of measurement, by using blood pressure percentiles for instance.

The mechanism behind the effect of birth weight on hypertension is not yet clear, but there are several hypotheses. Low birth weight is thought to affect hypertension through the development of a thrifty phenotype[60,61]. Vascular dysfunction due to impaired growth is another possible mechanism behind the impact of low birth weight on hypertension. A combination of low birth weight and post-natal weight gain could also cause a child to have an increased risk for developing hypertension[53]. permanent changes in metabolism and appite[98] caused by high birth weight and post-natal weight gain could also cause hypertension. It is important to investigate which possible mechanism are at work to find ways of intervening with the intention of preventing hypertension.

Placental dysfunction is a perinatal factor that causes foetal malnutrition. This malnutrition can cause cardiovascular problems in later life and placental dysfunction has been found to be a risk factor for developing hypertension[64-67]. Placental dysfunction can be diagnosed during pregnancy, it is therefore possible to think of therapies that tackle the associated malnutrition.

Late preterm infants are born between the 34th and 37th week of gestation. Late-preterm children have a higher risk, than children that are full-term, for developing hypertension. This is likely caused by the underdevelopment of the kidneys[71]. Problems can be caught early in these children by monitoring their blood pressure. In this way treatment can start early and prevent possible damage which can be caused by hypertension.

Maternal obesity is a risk factor for childhood hypertension[76]. Though it increases the risk for hypertension this appears to be caused by an increased risk for childhood obesity. Both these increased risks are in part because of foetal programming[76,110]. However family environment and genetic predisposition can not be excluded. Preventing obesity remains an important step in combatting hypertension.

Maternal smoking is associated with an increased risk for elevated blood pressure most likely through an underlying intrauterine mechanism. This mechanism is not yet clear though and further research is needed as it could find new pathways for intervention.

Taken together much research is still needed to further elucidate perinatal factors that influence childhood blood pressure. This is important because new treatments could evolve from this. Catching hypertension early might save many lives.

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Appendix

Appendix 1. Blood Pressure Levels for Boys by Age and Height Percentile

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	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	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	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	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	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	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	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	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	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	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	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	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	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	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	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	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	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	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	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

Appendix 1 (continued). Blood Pressure Levels for Boys by Age and Height Percentile

Age (Year)	BP Percentile ↓	Systolic BP (mmHg)							Diastolic BP (mmHg)						
		← Percentile of Height →							← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	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	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	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	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	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	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	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	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	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	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	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	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	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

NHLBI[8]. BP = blood pressure

Appendix 2. Blood Pressure Levels for Girls by Age and Height Percentile

Age (Year)	BP Percentile ↓	Systolic BP (mmHg)							Diastolic BP (mmHg)						
		← Percentile of Height →							← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	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	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	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	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	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	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	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	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	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	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	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	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	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	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	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	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	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	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	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

Appendix 2 (continued). Blood Pressure Levels for Girls by Age and Height Percentile

Age (Year)	BP Percentile ↓	Systolic BP (mmHg)							Diastolic BP (mmHg)						
		← Percentile of Height →							← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	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	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	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	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	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	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	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	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	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	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	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	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	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

NHLBI[8]. BP = blood pressure