CHAPTER 7

General Discussion
Introduction

This thesis describes the pathophysiology of hypertension in overweight and obese children; the prevalence of hypertension in Dutch overweight children; the process of screening and diagnosis; and the consequences of hypertension in overweight and obese children. This last chapter summarizes and discusses the main results of this thesis. In addition, methodological concerns and the relevance for clinical practice will be discussed. Furthermore, recommendations for further research will be provided.

Summary of main findings

Pathophysiology of hypertension in overweight and obese children

Chapter 2 provides an overview of factors which potentially play a role in the development of hypertension in overweight and obese children. The pathophysiology of hypertension is multifactorial, interdependent and complex, and is not yet completely understood. There seems to be a role for endocrine determinants, such as renin-angiotensin-aldosterone system (RAAS), corticosteroids and adiponectin. Sympathetic nervous system (hyper)activity and sodium retention seem also of influence on the development of hypertension in obese children, as well as oxidative stress, inflammation and endothelial dysfunction, but their role is complex and it is often difficult to distinguish between cause and effect. Several other factors have been discussed such as genetic factors, birth weight, altered sleep patterns and hyperuricemia. Most of these factors are not independently associated with hypertension, but interact with others at multiple levels, making the pathophysiology of hypertension in obesity difficult to grasp.

In chapter 3, the role of cortisol in the pathophysiology of hypertension in
overweight and obese children was explored, by analysing urine and saliva samples from hypertensive overweight, normotensive overweight, and normotensive non-overweight children. In our study sample, there were no significant differences in cortisol parameters between hypertensive and normotensive overweight children. However, overweight children had significantly higher urinary cortisol and cortisone levels than non-overweight children, indicating an increased HPA axis activity. Also, overweight children had a higher urinary cortisol-to-cortisone ratio than non-overweight children, which reflects decreased activity of 11β-HSD2, the enzyme which converts active cortisol into inert cortisone, and they had a lower early-morning peak cortisol.

**Prevalence of hypertension in Dutch overweight and obese children**

*Chapter 4* describes the prevalence of hypertension in Dutch overweight and obese children, and the influence of using different measurement protocols on prevalence rates. Many studies on the prevalence of hypertension use different measurement protocols to diagnose hypertension, resulting in a wide range of prevalence rates. There seems to be no consensus on how many times blood pressure should be measured and which value (e.g. the mean or the lowest value of measurements) should be compared with reference values. In our study population, looking at the first blood pressure measurement alone, 33% of overweight and 21% of non-overweight children had hypertension. By comparing the mean of the first two measurements with reference values, 28% of overweight children and 16% of non-overweight children had hypertension. Based on the lowest value of three consecutive measurements, the prevalence decreased to 12% among overweight children and 5% among non-overweight children at visit one, and at visit two 4% of overweight children still had hypertension.
Using the lowest value of three consecutive measurements at two occasions, the observed prevalence of hypertension in our sample of overweight and obese children was 4%, which is considerably lower than in recent literature using the first or mean blood pressure value (4–33%)(1-6). We recommend to measure blood pressure a third time if blood pressure is elevated the first two measurements. The third measurement in a row often provides the lowest value, probably due to reduced anxiety. In addition, we argue that taking the lowest value is the best approach to obtain the 'real' value, since blood pressure values can easily rise due to physical activity or anxiety, but blood pressure cannot easily drop below its normal level in a healthy child. Therefore, in clinical practice it is common to use the lowest value instead of the average. We recommend that researchers use the lowest values as well.

Childhood hypertension can lead to the development of atherosclerosis in young adulthood (7-9), which in turn can lead to cardiovascular morbidity and mortality and kidney damage (10). Therefore, despite the low prevalence, measuring blood pressure in all overweight children is recommended in view of preventing later consequences of hypertension. In addition, we recommend to study which measurement protocol generates the most accurate values of blood pressure by comparing them with ambulatory blood pressure measurements.

**Screening, diagnosis and treatment of hypertension in obese children**  
*Chapter 5* describes the different policies that paediatric nephrologist around the world use for screening, diagnosis and treatment of hypertension in obese children. To gain more insight in current practises regarding screening, diagnosing and treatment of hypertension in obese children by paediatric nephrologists, a questionnaire was sent to all members of the European
Society for Paediatric Nephrology. Although nearly 100% of the respondents agreed that screening of obese children for hypertension is indicated, it was current practice in only 56% of participating countries. A majority of the respondents (88%) diagnosed hypertension with 24-hour ambulatory blood pressure measurement. Which diagnostics are used to rule out causes or consequences of hypertension varied among the respondents, in particular whether or not plasma renin/aldosterone measurements or a dimercaptosuccinic acid (DMSA) renal scan are used. Regarding treatment of choice, 45% of the paediatric nephrologists preferred to start treatment with a lifestyle program, 2% with antihypertensive medication, and 40% with both. For 73% of the respondents, angiotensin-converting enzyme (ACE)- inhibitors or angiotensin receptor blockers were drugs of first choice.

The respondents provided several suggestions to improve screening, diagnosis and treatment of hypertension in obese children. These included the establishment of an adequate system for screening for hypertension in all obese children, for example at schools; increasing national awareness for obesity-induced hypertension as a serious public health problem; and the establishment of international guidelines on the screening, diagnosis and treatment of hypertension specific for obese children.

Hence, the findings of this study emphasize the urge and importance of an international guideline for screening, diagnosis and treatment of hypertension in obese children.

**Screening for kidney injury in overweight and obese children with hypertension**

The study in *chapter 6* explored the presence of kidney injury in overweight and obese children with hypertension. Urinary microalbumin levels were measured to assess presence of kidney injury. Moreover, the use of urinary
neutrophil gelatinase-associated lipocalin (NGAL) as a marker to detect kidney injury was explored. NGAL is a promising novel marker for chronic kidney injury, which indicates the severity and risk of progression of kidney injury both in adults and children (11;12).

In our study sample, there was no significant difference in presence of microalbuminuria nor NGAL levels between children with or without hypertension and between overweight and non-overweight children. Thus, in our sample no evident kidney injury was present in hypertensive overweight children. We cannot conclude on the usefulness of NGAL as a marker for chronic kidney injury in hypertensive overweight children. Remarkably, girls had significantly higher NGAL levels than boys, independent of age or BMI.

**Methodological concerns**

**Cross-sectional study design**

*Chapters 3, 4 and 5* describe studies with a cross-sectional design. Since cross-sectional studies are limited to describing associations, it is not possible to determine causal relationships. Longitudinal studies are needed to gain more insight in the development of hypertension; underlying mechanisms; and the development of consequences of hypertension such as kidney injury.

**Sample size**

The sample size for the studies with urine and saliva were small. Unfortunately it was difficult to collect large numbers of urine and saliva samples and it was especially difficult to recruit children who were obese and hypertensive. The small sample size also limits the generalizability of findings. In addition, children were selected by convenience sampling. This might have
let to sampling bias, the study sample might not be representative of the entire population.

**Blood pressure measurements**

According to general practice in Child Health Care, children were asked to return for a second set of measurements when their blood pressure was elevated at the first visit. Ideally, all children with elevated blood pressure at the second visit were measured a third time with 24-hour ambulatory blood pressure monitoring for a final diagnosis. Unfortunately 24-hour ambulatory blood pressure monitoring was performed in only 5% of children with elevated blood pressure at the second visit, due to no-show of children, unavailability of a 24-hour ambulatory blood pressure monitor or cuffs, or a normal blood pressure at the paediatric polyclinic or general practitioner.

Another concern might be that the blood pressure measurements in Child Health Care practice were performed by different physicians, nurses and physician assistants. Although all Child Health Care professionals received a training on performing standardized blood pressure measurements prior to the start of the study, and an oscillometric monitor instead of a sphygmomanometer was used, this may have led to some inter-observer variation.

**Compliance of parents and children**

Compliance of parents and children was an important issue in this study. Of the children who had elevated blood pressure at the first visit at Child Health Care and were asked to return for a second visit to measure blood pressure again, 14% did not show up at their second appointment. Of the children who did show up at the second visit and were referred to a general practitioner or paediatrician because of their elevated blood pressure, at least 12% did not
show up at this third appointment. Therefore, information on the exact prevalence of hypertension in this study population is not available.

It is surprising that when parents know that their child may have hypertension, they still withdraw from follow-up appointments. Unfortunately, we were unable to retrieve reasons of children and their parents for not-showing up at their follow-up appointments. Children who did not show up did not significantly differ from the children who did with respect to ethnicity, age or BMI. Compliance of children and their parents to obesity treatment programmes has proven to be difficult by other studies as well, showing drop-out rates ranging from 10 to 80% (13). In future studies more attention should be paid to reasons for no-show, e.g. lack of motivation or communication, and on strategies to increase compliance.

Relevance and implications for practice and future research

Implementation of screening

The Dutch ‘Guideline overweight for Child Health Care’ recommends to screen overweight children from the age of 5 for hypertension to prevent cardiovascular morbidity and kidney damage (14). To date, not all Child Health Care Institutions have implemented this recommendation to measure blood pressure. In view of the possible adverse consequences of hypertension, blood pressure measurements to screen for hypertension in overweight children will hopefully be widely implemented in the near future.

Monitoring blood pressure in overweight children enables early identification and treatment of hypertension. This supports the prevention of hypertension-induced renal insufficiency at a later age, thereby reducing the number of adults with end-stage kidney failure, and limiting healthcare costs. More
research is needed to study the exact costs of screening for hypertension in children and the benefits in health and costs on the long term.

**Blood pressure reference values**

Recent literature (1;15-17) debated whether separate reference values are needed for hypertension in overweight and obese children versus normal weight children. The reference values provided by the National High Blood Pressure Education Programme (NHBPEP) Working Group on Children and Adolescents are created based on the pooling of the first blood pressure measurement values of several international cohort studies in both non-overweight and overweight or obese children (18). Schwandt et al. (1) argue that since overweight and obese children have substantially higher blood pressure values, separate blood pressure percentiles for overweight and obese children should be installed to evaluate their blood pressure. This would allow overweight and obese children to have a higher normal blood pressure than non-overweight children (1). On the other hand, Urbina and Falkner (15) argue that an increased blood pressure imposes an increased risk for target organ damage and cardiovascular events (15). Since this holds for both normal weight as for overweight and obese children, they pose that separate reference values would intentionally expose overweight and obese children to higher risks for adverse outcomes of elevated blood pressure.

Based on the same grounds that overweight and obese children in general have higher blood pressure values, one could argue that reference values should be based on normal weight children alone. Using reference values based on both normal weight and overweight and obese children, as provided by the NHBPEP Working Group, bring about the risk that normal weight children with an elevated blood pressure are not identified, since overweight and obese children increase reference values (16). However, Schwandt et al.
(1) shows in his study of 22,051 children and adolescents (of which 3,134 overweight or obese children) that blood pressure percentiles for normal weight children alone and percentiles for the general population of children are almost identical (1). In addition, the risk of lowering reference values by removing overweight and obese children from the sample may lead to an overestimation of elevated blood pressures and possibly to overtreatment. Also it could create a disproportioned amount of anxiety regarding hypertension (17).

Additionally, it must be noted that the reference values for children are based on statistics and not on clinical outcomes, as is the case in adults (15). There is not much proof for the clinical relevance of the current reference values for children. More longitudinal research is needed to examine whether the childhood reference values for hypertension indeed indicate increased risk for organ damage and later cardiovascular events.

**Use of simplified reference values**

The NHBPEP Working Group has provided extensive reference values for blood pressure in children, according to height and gender (19). It has been reported that (pre)hypertension in children is greatly underdiagnosed, probably due to the complexity of the diagnostic criteria (20). In our study we have used simplified reference values, as presented in the ‘Guideline overweight for Child Health Care’ (14), which are not separated for gender and height. However, a correction of blood pressure for height is possible: if height is -2 SD, systolic blood pressure values can be adjusted with -3 mmHg and diastolic values with -2 mm Hg; and if height is +2 SD, systolic blood values can be adjusted with +3 mmHg and diastolic values with +2 mm Hg. We found a rather large discordance in prevalence of hypertension between the
simplified reference values used by the Child Health Care professionals and the reference values provided by the NHBPEP Working Group (19). Of the children who had hypertension according to the simplified reference values, 69.4% also had hypertension according to the reference values provided by the NHBPEP Working Group. Hence, the simplified reference values resulted in an overestimation of the prevalence of hypertension. This is in line with several other studies who composed and tested simplified reference values based on the NHBPEP Working Group that also found high numbers of false-positives (21,22). One study composed simplified reference values for blood pressure for height but not gender. They found that 65–81% of children with normal blood pressure were labelled as hypertensive. The sensitivity was nearly 100% (21). Another study created simplified reference values classified for gender, but not height, and found many false-positives as well. The sensitivity was 100%, all children with hypertension were identified (22). More research should be done on the development of simplified reference values which should focus on the balance between the risk of underdiagnoses of hypertension in children versus ease-of-use for healthcare workers with more false-positives.

**White coat hypertension**

In our study, in case of elevated blood pressure, children were asked to return for a second visit within 6 weeks after the first, to measure the blood pressure again for three consecutive times. This way, children with ‘white coat hypertension’ were filtered out. Of the overweight children that returned for a second visit, only 38% had high blood pressure again. This is an interesting and novel finding. It would be interesting to study whether the blood pressure of the 62% of children who did not have hypertension at the second visit had really an improved blood pressure, e.g. due to changes in lifestyle (lower salt
intake, more sleep), or more likely, that the children were more relaxed at the second visit.

**Prehypertension**

In our sample the prevalence of hypertension, defined as blood pressure above 95\textsuperscript{th} percentile, among overweight or obese children was only 4.4%. However, children with a blood pressure above the 90\textsuperscript{th} percentile, which is the definition for prehypertension, seem to already have an increased risk for cardiovascular diseases and kidney injury (23). Therefore the NHBPEP Working Group recommends to follow-up on children with a blood pressure ≥P90 within six months to measure blood pressure again. In addition, it is advisable to counsel these children on obtaining a healthy lifestyle, to prevent the development of hypertension and related comorbidity (19). Preferably this will also be implemented in Child Health Care. It should be evaluated whether this is feasible.

**Focus on integrated care**

The ‘Guideline overweight for Child Health Care’ (14), recommends the screening for hypertension in overweight children, and based on our study we support this recommendation. Once overweight children with hypertension are identified through screening, they must undergo diagnostic tests to rule out certain causes and consequences of hypertension and, if necessary, receive adequate treatment. However, it would be useless to identify children with elevated blood pressure through screening, if there is no adequate follow-up care arranged. General practitioners and paediatricians should be aware of hypertension in overweight and obese children, they must have the right equipment at their disposal, such as a 24-hour ambulatory blood pressure monitor and the right cuff sizes and there should be a clear protocol
for which diagnostic tests to perform and for adequate treatment and aftercare. Hence, there is need for a focus and consensus on integrated care including Child Health Care, general practitioners, paediatricians and paediatric nephrologists regarding hypertension in overweight and obese children.

Regarding adequate treatment, lifestyle intervention with focus on physical activity and weight loss is recommended. If there is an insufficient response to the lifestyle intervention, pharmacological treatment is indicated (19). It would be interesting to study the effectiveness of a lifestyle programme versus pharmacological treatment for hypertension in overweight and obese children, in a randomized controlled trial.

**Focus on motivation of parents and children**

In order for the ‘Guideline overweight for Child Health Care’ to be successfully implemented and executed, it is important that parents and their children show up at appointments with Child Health Care, the general practitioner or paediatrician. It is important to learn more about the reasons why parents do not show up (e.g. perceived barriers) in qualitative research. More information to parents on childhood hypertension and its possible consequences may motivate parents to undertake action.

In a previous study a bottleneck analysis was performed regarding screening for hypertension in overweight and obese children in Dutch Child Health Care (24). By means of focus groups and an online questionnaire, Child Health Care professionals were asked about their experiences with measuring blood pressure. A frequently mentioned advantage of measuring blood pressure is that professionals experienced that parents took their child’s weight status more serious after the blood pressure has been measured, regardless of the outcome of the blood pressure measurements. Because of the blood pressure
measurements, their child’s overweight apparently became a medical concern motivating them to undertake action. It has not been evaluated whether changes in weight were actually achieved. Hence, measuring blood pressure could function as a motivational tool to improve compliance to interventions targeting a healthy weight (24).

**Future research**

Longitudinal studies are needed to gain more insight in the pathophysiology of hypertension in overweight and obese children. Knowledge on the mechanisms responsible for the development of hypertension could lead to more effective treatment options. In addition, longitudinal cohort studies are necessary to study the possible consequences of hypertension in overweight and obese children. Since consequences of hypertension such as kidney injury do not develop overnight, it would be interesting to follow a cohort of overweight or obese children with and without hypertension over a longer period of time. By monitoring the development of kidney injury possible risk factors could be identified.

Additional research should be directed at the evaluation of reference values for hypertension in children, and whether they correctly indicate an increased risk for organ damage and later cardiovascular events.

**Conclusion**

This thesis aimed to extend the knowledge on hypertension in overweight and obese children, and to describe the pathophysiology, the consequences, and the process of screening, diagnosis and treatment of hypertension in overweight and obese children.
The prevalence of hypertension is highly dependent on the measurement protocols used. Based on our protocol, i.e. the lowest value of three consecutive measurements at two different occasions, the observed prevalence of hypertension in our sample of overweight children was 4%. However, as the clinical consequences of hypertension in children are serious, screening for hypertension in overweight and obese children is still recommended. In addition, since the causes of overweight-induced hypertension and secondary hypertension are different, there is need for an international guideline for screening, diagnosis and treatment of hypertension in obese children.

The pathophysiology of hypertension in overweight and obese children is complex, many factors play a role that are often interdependent. Longitudinal studies are necessary to gain more insight in the pathophysiology of hypertension in overweight and obese children to optimize targeted treatment and to study the development of kidney injury as a consequence of hypertension in overweight and obese children.
Reference List


(22) Kaelber DC, Pickett F. Simple table to identify children and adolescents needing further evaluation of blood pressure. *Pediatrics* 2009;123:e972-e974.
