Summary
SUMMARY

Childhood overweight and obesity is a major public health problem. A pressing concern with overweight and obesity is that it is strongly associated with hypertension (high blood pressure). Studies found a prevalence of hypertension ranging from 4–14% in overweight children to 11–33% in obese children, making overweight and obesity the number one cause of childhood hypertension in current times.

Untreated childhood hypertension can have serious consequences. Firstly, childhood hypertension can lead to atherosclerosis already in young adulthood, which in turn can lead to cardiovascular morbidity and mortality and to kidney damage. Secondly, since obesity and hypertension have the tendency to track from childhood into adulthood, the burden of hypertension in adults will rise as well. Therefore, it is important that hypertension is timely identified and treated.

This thesis presents a study of hypertension in overweight and obese children, it’s pathophysiology, consequences, and the current process of screening, diagnosis and treatment.

**Pathophysiology of hypertension in overweight and obese children**

Since the causes of hypertension in overweight and obese children remain partly unclear, a deeper understanding of its pathophysiology is needed to create more targeted and effective detection and treatment strategies. In a systematic literature search in chapter 2, we therefore explored factors that play a role in the development of hypertension in overweight and obese children. Some studies suggested a role for endocrine determinants, such as renin-angiotensin-aldosterone system (RAAS), corticosteroids and adiponectin. Also sympathetic nervous system (hyper)activity and sodium retention seem of influence, as well as oxidative stress, inflammation and
endothelial dysfunction. Several other factors have been suggested, such as genetic factors, birth weight, altered sleep patterns and hyperuricemia, an excess of uric acid in the blood.

The role of these factors is complex because they are often not independently associated with hypertension, but interact with each other at multiple levels. In addition, since most studies are of a cross-sectional nature, meaning that they provide data of one moment in time only, it is not possible to distinguish between cause and effect. Therefore we recommend to conduct longitudinal studies, in which children are followed for a longer period of time, to gain more insight into the complex mechanisms behind the development of hypertension in overweight and obese children.

Several studies also suggested a role for cortisol in the development of hypertension in children with overweight and obesity. To study this association in chapter 3 we collected urine (n=180) and saliva (n=126) samples from children aged 5 to 17 years with and without overweight and obesity, and with and without hypertension. Urine and saliva were analysed for cortisol and cortisone. Overweight children had significantly higher urinary cortisol and cortisone levels than non-overweight children, indicating an increased hypothalamic–pituitary–adrenal (HPA) axis activity. Also, overweight children had a higher urinary cortisol-to-cortisone ratio than non-overweight children, reflecting a decreased activity of 11 β-hydroxysteroid dehydrogenases-2 (11β-HSD2), the enzyme which converts active cortisol into inert cortisone. However, we could not find an indication for a role for cortisol in the pathophysiology of obesity-induced hypertension, since in our research there were no significant differences in cortisol parameters between overweight children with and without hypertension.
Prevalence of hypertension in Dutch overweight and obese children

The Dutch ‘Guideline overweight for Child Health Care’ recommends screening overweight children from the age of 5 years for hypertension to prevent cardiovascular morbidity and kidney damage. In chapter 4 we assessed the prevalence of hypertension in Dutch overweight and obese children using different methods of assessing blood pressure.

The prevalence of hypertension is highly dependent on the definitions and criteria used for interpreting blood pressure, i.e. how many measurements are taken and which value (e.g. the mean or the lowest value of measurements) is compared with reference values. In a group of children with overweight (n=969) and without overweight (n=438) we measured blood pressure three consecutive times. All children with elevated blood pressure were asked in on a second visit to measure blood pressure again three consecutive times. Subsequently we compared three different classification methods of hypertension.

1) Based on the first blood pressure measurement alone, 33% of overweight and 21% of non-overweight children were classified as having elevated blood pressure. 2) Based on the mean of the first two measurements, a method most often used in literature, 26% of overweight children and 14% of non-overweight children were classified as having elevated blood pressure.

3) Based on the lowest of three consecutive measurements, 12% of overweight children and 5% of non-overweight children at visit one, and only 4% of overweight children at visit two were classified as having elevated blood pressure and none of the non-overweight children.

We believe this last method of assessing blood pressure is the most accurate since blood pressure may easily rise due to anxiety, stress or illness, but
cannot easily fall below its normal value. Therefore, we hypothesize that using the lowest value is the best approximation of the actual blood pressure.

Using this last definition of high blood pressure, the prevalence was considerably lower than reported in literature. Despite the relatively low prevalence, we recommend to measure blood pressure in all overweight children as with this rather small investment, potential subsequent cardiovascular morbidity and mortality and kidney damage in these children can be traced possibly prevented.

**Screening, diagnosis and treatment of hypertension in obese children**

Hypertension in children as a result of obesity may need a different approach than hypertension as the result of a different underlying cause, such as a kidney disease. In *chapter 5* we evaluated current policies of paediatric nephrologists around the world regarding screening, diagnosis and treatment of hypertension in obese children with an online questionnaire. Although nearly all respondents (n=214) agreed that obese children should be screened for hypertension, screening was current practice in only 56% of participating countries. For diagnosis of hypertension, the majority of respondents (88%) used 24-hour ambulatory blood pressure measurement. Diagnostics used to rule out causes or consequences of hypertension varied among the respondents, especially the use of serum renin/aldosterone, urine sodium/potassium, and the use of a DMSA scan. Of the respondents, 45% preferred to start treatment of hypertension in obese children with a lifestyle program, 2% with antihypertensive medication, and 40% with both. For 73% of the respondents, ACE-inhibitors or angiotensin receptor blockers were drugs of first choice.

Our results showed that policies concerning screening, diagnosis and treatment of hypertension in obese children varied widely. This variation in
policies emphasizes the urge and importance of *more research* and the *development of an international guideline* regarding the preferred methods for screening, diagnosis and treatment of hypertension in obese children.

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

Untreated hypertension can lead to kidney damage. In *chapter 6* we evaluated if kidney damage is in fact present in overweight and obese hypertensive children by collecting urine samples (*n*=180) from hypertensive overweight, normotensive overweight, and normotensive non-overweight children, aged 5–17 years. We also evaluated whether neutrophil gelatinase-associated lipocalin (NGAL) is a suitable marker to detect chronic kidney damage in children. NGAL is a relatively new marker mainly used to detect acute kidney damage, but seems promising in detecting chronic kidney damage as well. In addition to NGAL, urine was analysed for microalbuminuria, also a measure of kidney damage.

However, we found no significant differences in NGAL levels or the presence of microalbuminuria between the three study groups. Based on urine microalbumin and NGAL levels no evident kidney damage was present in hypertensive overweight children in our study. Based on these results, we could not conclude on the usefulness of NGAL as a marker for chronic kidney damage in children with obesity and hypertension.

**Conclusion**

The prevalence of hypertension in children with overweight or obesity was lower than expected using a stricter, and more accurate, classification of hypertension. Nevertheless, we still recommend to measure blood pressure in children with overweight and obesity considering the possible damaging
consequences of untreated hypertension. Kidney damage, one of the possible consequences, was not detectable in our study sample. To gain more insight in the development of kidney damage in overweight or obese children with hypertension it is necessary to follow these children for a longer period of time. In addition, long-term studies are also needed to gain deeper understanding of the causes of the development of hypertension in overweight or obese children and to develop more targeted and effective detection and treatment strategies for childhood hypertension.