CHAPTER 1

General Introduction
Childhood overweight and obesity

Worldwide the prevalence of overweight and obesity has increased persistently in the last decades: in 2010, an estimated 40 million children under the age of five were overweight (1). In the United States 17% of children aged 2–19 years were obese (2), in European countries the prevalence of childhood overweight was between 13 and 28%, and of obesity between 2 and 13% (3-8). In addition to the increasing incidence of obesity in children, its severity is increasing as well. The prevalence of severe obesity has tripled over the past 25 years (9).

The growing epidemic of obesity in children and adolescents is not without consequences. Obesity in children can lead to the development of several diseases such as type 2 diabetes mellitus, and an unfavourable cardiovascular risk profile including high blood pressure, high low-density-lipoprotein (LDL) cholesterol levels and triglycerides, low high-density-lipoprotein (HDL) cholesterol levels, and high levels of fasting insulin (10). In a group of children, 2–18 years, attending a special outpatient clinic for obesity, over 90% had at least one or more cardiovascular risk factors such as hypertension, elevated glucose, insulin resistance and an abnormal lipid profile (11). In parallel with the increase in obesity, hypertension is increasingly diagnosed in children and adolescents (12-17). Therefore, overweight and obesity in children are a major public health concern.

Hypertension in overweight and obese children

Many studies found an association between hypertension and overweight and obesity in children. The prevalence of hypertension in these studies ranged from 4–14% in overweight children to 11–33% in obese children (12-17).
CHAPTER 1

Currently, overweight and obesity are the main causes for childhood hypertension, in contrast to the 1980s when secondary hypertension, hypertension caused by an identifiable underlying secondary cause, represented 84% of the cases of hypertension. Hence, the ratio between secondary and primary hypertension has shifted in the last decades (18). In addition, since obesity and hypertension have the tendency to track from childhood into adulthood, the burden of hypertension in adults will steadily increase as well (19;20).

The mechanisms behind the development of hypertension in obese children are not yet completely understood. Suggested mechanisms for the pathophysiology of hypertension include sympathetic activation via hyperleptinemia and hyperinsulinemia, vascular damage as a consequence of inflammation, endothelial dysfunction and oxidative stress, and activation of the renin-angiotensin system. Often these mechanisms are interdependent and complex (21-23). To be able to effectively treat hypertension in obese children, it is important to gain better understanding of the pathophysiology of hypertension in this population.

Childhood hypertension can lead to the development of atherosclerosis in young adulthood (24-26). Atherosclerosis in turn can result in ischemia, myocardial and cerebral infarction, and renal failure (27). Therefore, it is important that hypertension is timely identified and treated. Preventive screening for hypertension in those who are at risk – overweight and obese children – may be necessary to avert a generation of young adults suffering from cardiovascular and kidney disease.

Hypertension is suggested to be one of the most important causes of end-stage renal injury in adult patients (28). In addition, it has been suggested that in adults, since the beginning of the increasing obesity epidemic, the incidence
of kidney injury has increased (29-32). However, little is known about the presence of kidney injury in hypertensive overweight and obese children.

An early sign of kidney injury is the presence of abnormal levels of urinary (micro)albumin. Kidney injury caused by hypertension can also be detected by the presence of microalbuminuria, as a consequence of hypertension-induced glomerular damage (33-35). Microalbuminuria is a strong predictor of renal and cardiovascular morbidity and mortality in adults with hypertension (36). In 20% of children with 24 hour ambulatory blood pressure measurement (ABPM) confirmed hypertension, microalbuminuria was found (36). In the last few years, neutrophil gelatinase-associated lipocalin (NGAL) has been discovered as a biomarker for acute kidney injury, and seems to be a promising marker for chronic kidney injury as well, both in adults and children (35;37-39). More research is needed to evaluate the use of NGAL as a marker for chronic kidney injury in hypertensive obese children.

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

Although many studies have shown an association between overweight, obesity and hypertension in children, several questions regarding screening, diagnosis and treatment of hypertension in overweight and obese children remain unanswered in current guidelines: Should all overweight children be screened for hypertension? Which diagnostic tests are needed to determine hypertension? Which tests are required to exclude possible causes – other than overweight or obesity – of hypertension? Which consequences of hypertension should be checked? Which treatment is preferred? How should follow-up of hypertensive obese children be arranged and by whom? In the Netherlands, Child Health Care reaches 95% of all children at different ages. It
provides a unique setting for prevention and screening. Child Health Care offers voluntary routine medical examinations in which it tracks weight, height and development of children from birth until the age of 18 years (40;41). Screening of overweight children from the age of 5 for hypertension by Child Health Care to prevent kidney damage and cardiovascular morbidity at a later age is recommended in the ‘Guideline overweight for Child Health Care’ [JGZ-Richtlijn Overgewicht], published in May 2012 (42). It needs to be evaluated whether screening for hypertension in Child Health Care is worthwhile.

Once obese children with hypertension are identified through screening, they must undergo diagnostic tests and, if necessary, receive adequate treatment. However, hypertension in obese children – often referred to as primary hypertension – may need a different approach to diagnosis and treatment than children with secondary hypertension. Obesity-induced hypertension is often less severe and manifests itself often with less symptoms in comparison to secondary hypertension (43). Therefore, some examinations to rule out consequences of hypertension might not be necessary, for example, a consultation with an ophthalmologist to check for hypertensive retinopathy. There are also differences in preferred treatment between obesity-induced hypertension and secondary hypertension. Lifestyle intervention might suffice as treatment for obesity-induced hypertension, whereas secondary hypertension most likely needs pharmacological treatment (44).

Despite the apparent differences between primary and secondary hypertension, there is neither consensus nor a clear guideline regarding screening, diagnosis or treatment of hypertension specific for obese children. Hence, there is need for such a guideline with a focus on integrated care with Child Health Care, general practitioners, paediatricians and paediatric nephrologists.
Aim and outline of this thesis

The research described in this thesis aimed to extend the knowledge on hypertension in overweight and obese children; the pathophysiology, the consequences, and the optimal process of screening, diagnosis and treatment. Chapter 2 describes a systematic literature review summarizing the evidence on different potential mechanisms in the pathophysiology of hypertension in overweight and obese children. Chapter 3 explores the role of cortisol in the pathophysiology of hypertension in overweight and obese children. Chapter 4 describes the prevalence of hypertension in a sample of Dutch overweight and obese children and discusses different methods and criteria for the diagnosis of hypertension. Next, chapter 5 presents the results of a survey on current practices regarding screening, diagnosis and treatment of hypertension in obese children among paediatric nephrologist around the world. Chapter 6 focuses on the presence of kidney injury in overweight and obese hypertensive children and on the question whether NGAL is a suitable marker for chronic kidney injury in obese children. Finally, chapter 7, summarizes and critically discusses the main findings of this thesis and implications for clinical practice. In addition, an overall conclusion is provided as well as recommendations for future research.
CHAPTER 1

Reference List

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