Summary

In this thesis we have investigated the relationships among birth weight, microvascular function and cardiovascular risk factors (figure 1). The microcirculation is important in determining the peripheral vascular resistance as well as the delivery of nutrients to the tissues. An impaired microvascular function may therefore be important in the development of high blood pressure and insulin resistance, both of which are associated with increased cardiovascular risk. Low birth weight is also associated with an increased cardiovascular risk. This association is probably mediated by the association of low birth weight with high blood pressure, insulin resistance and other cardiovascular risk factors. In addition, it has been suggested that an impaired microvascular function is related to a lower birth weight. In view of these findings, a better understanding of the relationships among birth weight, microvascular function and cardiovascular risk factors may contribute to prevention of cardiovascular disease and reveal new therapeutic targets.

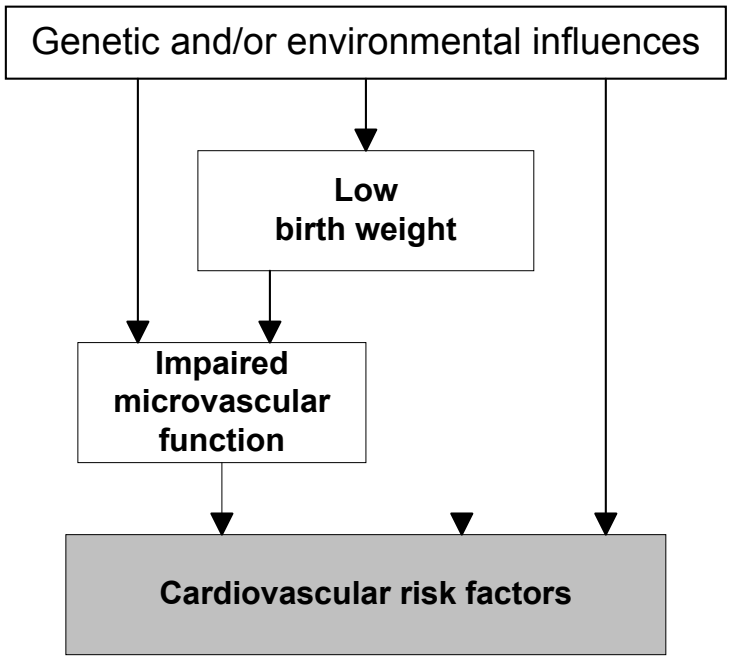

Figure 1. The postulated relations among birth weight, microvascular function and cardiovascular risk factors. Both birth weight and microvascular function are related to cardiovascular risk factors, and microvascular function may link birth weight with cardiovascular risk. All of these variables may be influenced by genetic and/or environmental influences.

Part 1 Birth weight and microvascular function

Epidemiological studies have consistently demonstrated that weight at birth is negatively associated with blood pressure and insulin resistance in adult life. Regardless of whether or not the origin of these relationships is genetic or environmental, alterations in microvascular function may be a possible mechanism explaining these associations. We have previously demonstrated that capillary recruitment during post-occlusive reactive hyperaemia was related to birth weight, blood pressure and insulin sensitivity in adults, but it could not be resolved whether the impaired capillary recruitment in subjects with a low birth weight was a cause or a consequence of the higher blood pressure and/or insulin resistance. In a study of prepubertal children, we found that birth weight was associated with capillary recruitment, but not with blood pressure or insulin sensitivity (Chapter 2). These data suggest that an impairment in capillary recruitment is a primary disturbance in individuals with a low birth weight, and is not secondary to higher blood pressure and/or insulin resistance. Changes in microvascular function may be a potential mechanistic explanation for the association of birth weight with blood pressure and insulin resistance.

Part 2 Microvascular function and cardiovascular risk factors

Insulin-mediated changes in muscle perfusion have been proposed to modulate insulin-mediated glucose uptake. We have investigated the effect of insulin on the microcirculation which may permit such modulation. Systemic hyperinsulinaemia induced recruitment of capillaries in skin, augmented nitric-oxide-mediated vasodilatation and influenced vasomotion in skin (Chapter 3). In addition, locally administered insulin induced a rapid increase in total skin blood flow, independent of systemic effects. These findings offer a potential physiological framework for further study of the functional coupling between insulin's metabolic and vascular actions.

Microvascular function has also been proposed as a possible mechanism explaining the association of acute smoking with an increased blood pressure and a decreased insulin sensitivity. We have examined the acute effects of smoking on skin microcirculatory function (Chapter 4). Acute smoking was associated with an impaired recruitment of capillaries and an impaired microvascular endothelium-dependent vasodilatation, whereas endothelium-independent vasodilation was not influenced. These findings are consistent with the hypothesis that the association of acute smoking with an increased blood pressure and a decreased insulin sensitivity is due to changes in microvascular function.

The inflammatory cytokine tumour necrosis factor α (TNF-α) has been reported to play an important role in insulin resistance. The mechanism by which TNF-α may cause insulin resistance is not clear. It has been suggested that TNF-α causes defects in capillary function, with a decreased access of insulin and glucose to tissues. To test this hypothesis, we assessed plasma TNF-α levels, skin capillary recruitment during post-occlusive reactive hyperaemia and insulin sensitivity in healthy adult individuals

(Chapter 5). In addition, to investigate whether these associations are already present in prepubertal children, we measured these variables in 21 of their children. TNF-α was associated with capillary recruitment during post-occlusive hyperaemia in adults. In addition, this capillary recruitment could partly explain the relationship between TNF-α and insulin resistance. Our findings thus provide support for a vascular component of TNF-α-induced insulin resistance. These associations, however, were not present in the prepubertal children. Our findings therefore suggest that the relationships among TNF-α, vascular function and insulin sensitivity are initiated during growth from childhood to adulthood.

Coronary microvascular disease may explain the occurrence of myocardial ischaemia without overt coronary artery blockage, as well as heart failure and mortality after myocardial infarction. However, methods to assess the coronary microcirculation are invasive and applicable only in experimental settings. The skin microcirculation offers an opportunity to noninvasively explore the relation of systemic microvascular dysfunction to (risk factors for) coronary heart disease. In our study, coronary heart disease risk was assessed with the use of the coronary heart disease risk score according to the Framingham Heart Study. We found that an increased coronary heart disease risk was associated with a lower endothelium-dependent vasodilatation and capillary recruitment in skin (Chapter 6). Our findings thus suggest that microvascular function in skin may be a valid model for the study of the relationships between cardiovascular risk factors on the one hand and microvascular function on the other.

Part 3 Birth weight and cardiovascular risk factors in twins

In Chapter 7 we have postulated that twin studies offer a unique opportunity to distinguish between intrauterine and genetic origins of the association between birth weight and cardiovascular risk factors in later life. We have discussed several advantages and limitations of the use of twin studies to investigate the influence of intrauterine and genetic factors. We have also emphasized that the comparison of within-pair analyses with unpaired analyses cannot be used to identify maternal influences on the association between birth weight and cardiovascular risk factors.

Many epidemiological studies have shown an inverse association between birth weight and blood pressure. To examine whether this association is explained by intrauterine or genetic factors, we have investigated birth weight and blood pressure in dizygotic and monozygotic adolescent twin pairs (Chapter 8). Intrapair differences in birth weight were negatively associated with differences in blood pressure in dizygotic twins, but not in monozygotic twins. This difference in the birth weight-blood pressure relationship between dizygotic and monozygotic twin pairs suggests that genetic factors may play an important role in the association between birth weight and blood pressure. Alterations in sympathetic and parasympathetic activity may be important mechanisms

explaining this birth weight-blood pressure relationship. We showed that low birth weight is associated with increased sympathetic activity, and that a large part of the association between birth weight and blood pressure is explained by this increase (Chapter 9). In addition, the within-pair analyses demonstrated that the association between birth weight and sympathetic activity was present in dizygotic twins but not in monozygotic twins, suggesting that the association between low birth weight and an increased sympathetic activity also depends on genetic factors. Birth weight was not associated with parasympathetic activity.

In a subgroup of this twin cohort, we found that intrapair differences in birth weight were negatively associated with differences in insulin resistance in both dizygotic twins and monozygotic twins (Chapter 10). This association was significant within monozygotic twins. These data suggest that the association between low birth weight and insulin resistance is not entirely due to a common genetic factor. Therefore, the association between these two variables appears, at least in part, due to intrauterine factors.

Low birth weight was associated with high total and LDL cholesterol within dizygotic twin pairs, but with low total and LDL cholesterol within monozygotic twin pairs (Chapter 11). In addition, low birth weight was associated with high fibrinogen within dizygotic twin pairs, but not within monozygotic twin pairs (Chapter 13). These data suggest that the association of birth weight with these cardiovascular risk factors is strongly influenced by the elimination of genetic factors (as achieved by using differences within monozygotic twin pairs). On the other hand, intrapair differences in birth weight were positively associated with differences in HDL cholesterol in both dizygotic and monozygotic twins. These data suggest that the association between birth weight and levels of HDL cholesterol may be independent of genetic factors. Plasma levels of lathosterol, campesterol and β-sitosterol, which are indicators of cholesterol synthesis and absorption, did not explain the association of low birth weight with high levels of total and LDL cholesterol. (Chapter 12), suggesting that these associations may be due, instead, to a decrease in cholesterol clearance.

Finally, intrapair differences in birth weight were significantly associated with differences in height in both monozygotic and dizygotic twins in adolescence (Chapter 14). The results were similar for data on adult height after 12 years of follow-up in a subgroup of these twin pairs. These data suggest that the association between size at birth and height in later life is in part due to intrauterine factors.