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PART 3

Main findings
CHAPTER 8

Summary, general discussion, and directions for future research
8.1 SUMMARY

In South Asian populations worldwide type 2 diabetes mellitus and cardiovascular diseases (together called cardiometabolic diseases) are more prevalent than in most other ethnic groups. These diseases generally develop at a lower BMI than in other ethnic groups, because South Asian adults generally have a body composition with a larger fat mass but simultaneously a smaller lean body (muscle and bone) mass at similar BMI levels compared with other ethnic groups. This is often called a ‘thin-fat’ body composition. Therefore, in India the universally used BMI cut-offs to detect overweight and obesity in adults were lowered from 25 to 23 kg/m² and from 30 to 25 kg/m² respectively, as these values show a better agreement with the increased cardiometabolic risks than the universal BMI-cut-off values.

Also in South Asian babies, children and adolescents cardiometabolic risks were shown to be increased at a lower weight or BMI. Several sets of lowered BMI cut-offs were proposed for the assessment of the nutritional status and associated health risks in South Asian children, but consensus has not been reached about the appropriateness of such cut-offs. In addition, it is unclear if (universal) growth standards to assess length and height such as the WHO references adequately describe growth in a prosperous South Asian population living in a western country. Normal values of weight, height, and BMI of affluent South Asian children living in a western country are currently not available.

The aims of this thesis were firstly, to find epidemiological evidence to support the hypothesis that affluent South Asian children living in a Western country are lighter and shorter than children from other ethnic groups, as such evidence could support the use of adjusted growth standards and anthropometric indicators for South Asian children.

Secondly, to develop South Asian specific height-for-age (0-20 years) and BMI-for-age (2-18 years) references and compare these with other (universal) references, and thirdly, to determine appropriate BMI cut-off values for thinness, overweight and obesity for South Asian children 2-18 years, and compare these with other sets of BMI criteria. Achieving these aims will likely contribute to a better understanding of which anthropometric values are to be considered normal for South Asians. Furthermore, the application of ethnic specific growth references and cut-offs is expected to allow for a better assessment of height and BMI in this group, of which the latter may aid in the prevention of diabetes and cardiovascular diseases in South Asians.

PART 1 - Epidemiology

In chapter 2 it was shown that the mean birth weight of South Asian babies did not change over a period of 35 years, while in 2006-2009 it was around 450 grams lower than in Dutch neonates. Based on universal birth weight standards the prevalence of low birth weight and small-for-gestational-age was very high. However, relative to ethnic specific standards the rates were concordant with those found in Dutch babies. Despite the stability of the birth weight of South Asian neonates over the studied period, South Asian babies have generally gained weight since the 1970s, indicated by a decrease in the prevalence of small-for-gestational-age over the studied
The study described in chapter 3 showed that a reference cohort of Surinamese South Asian children in the Netherlands aged 3-15 years, born before the obesity epidemic (1974-1976), also had a considerably lower mean BMI z-score than the “standard” population of WHO. In particular, the total prevalence of thinness, based on universal (WHO) cut-off criteria, was disproportionately high with rates of 36-38%, while simultaneously the overweight (including obesity) rates were very low (6-9%). Also in a cohort of South Asian children born in the Netherlands during the obesity epidemic (1991-1993) the thinness prevalence was high (24%), but now combined with high overweight rates (18-23%). These findings suggest that current universal BMI cut-offs overestimate thinness and, despite the apparently high rate found in the recent cohort, underestimate overweight in this population, rendering these cut-offs unsuitable for assessing the nutritional status of South Asian children.

The idea that universal cut-offs underestimate overweight and obesity in South Asian children was also supported by findings from a contemporary population of South Asian children. Mean BMI z-score (based on universal BMI references) in this group was found to be much lower than of Dutch, Turkish, and Moroccan children (chapter 5), and the prevalence of overweight (including obesity) was only slightly higher than in Dutch children (chapters 4 and 5), which is likely to represent an underestimate of the true cardiovascular and metabolic risks in the South Asian group.

PART 2 - Growth references

Chapter 6 presents height-for-age charts based on height of South Asian children in the Netherlands. The growth pattern of this ethnic group, as indicated by the shape of the height-for-age charts, was similar to that of a contemporary population of children in India. In particular, the height-for-age charts of a historical cohort of South Asian children in the Netherlands, born between 1974 and 1976, coincided largely with current Asian Indian height-for-age charts, suggesting a similar genetic make-up. Contemporary South Asian children in the Netherlands were taller at every age than those Asian Indian children, which may be attributable to differences in socioeconomic and environmental factors.

Compared to Dutch children South Asian children in the Netherlands were on average 0.5-0.6 standard deviation (SD) shorter up to the age of 14 years in boys and 12 years in girls, after which the differences increased to 1.5 to 1.7 SD at 20 years of age. The final height at 20 years of South Asian boys was 10 cm shorter than in their Dutch counterparts. In girls the difference in final height was 11 cm.

Larger discrepancies in growth patterns were found between the South Asian and the WHO height references over the whole age range. Between birth and the age of 5 years South Asian children in the Netherlands were 0.1 to 1.1 SD shorter than the “standard” WHO population. However, from the age of 5 years, boys were 0.1 to 0.6 SD taller till 14 years of age and girls 0.2 to 0.4 SD till the age of 12, after which the WHO population became increasingly taller. The difference in final height was 3 cm in boys and 4 cm in girls.

Menarche in South Asian girls is about 1.7 years earlier than in Dutch girls, which may account
for the 11 cm difference in final height between these two groups. The final height of South Asian children is 3 cm shorter than of Turkish and Moroccan children and 3-4 cm shorter than found in the WHO population. Because of these differences, it is doubtful whether universal height-for-age references may work well to assess the height of South Asian children. 

Chapter 7 provides BMI-for-age references based on a reference cohort of Surinamese South Asian children born between 1974 and 1976 (before the obesity epidemic). Compared with current Asian Indian BMI references the BMI was similarly distributed, although the mean BMI in South Asian in the Netherlands was lower and the distribution showed less variation. In the same study BMI cut-offs for overweight and obesity were created to correspond, at 18 years of age, with the adult BMI cut-offs of 23 kg/m² for overweight and 25 kg/m² for obesity which were previously proposed to be used for Asian Indian populations. A BMI of 15 kg/m² at 18 years of age was chosen as cut-off to determine thinness as this value corresponded in girls with the commonly used -2 SD criterion and because similarly to the lowered overweight cut-offs this value was 2 BMI-points lower than the universal cut-off for thinness. However, in boys a BMI of 15 kg/m² corresponded with the 7th percentile. The application of these South Asian specific BMI criteria is expected to better reflect their body composition which aids in the proper assessment of the nutritional status of this group, at least in the Netherlands.

8.2 GENERAL DISCUSSION: THE RELATION BETWEEN BODY COMPOSITION AND CARDIOMETABOLIC RISKS IN SOUTH ASIANS

Overnutrition and cardiometabolic risks
The human body composition can be described at several levels: I. atomic, II molecular, III cellular, IV tissue, and V whole body. The use of weight or BMI references can be regarded as a level V (whole body) description. Nevertheless, BMI-for-age, as in this thesis, is commonly used to estimate the body composition at the tissue level (figure 1), because it is highly correlated with the fat mass, easy to use, inexpensive and non-invasive. However, the sensitivity for identifying children with a high fat mass or increased cardiometabolic risks is moderate to high, depending on the population. As BMI is unable to properly distinguish between the fat mass and the fat-free (lean) mass, it is unlikely to reach a very high sensitivity. The fat mass simply varies too much at the same BMI level. In addition, the use of universal BMI-for-age references and cut-offs further limits the sensitivity in certain ethnic groups, as the relation between BMI and the fat mass, and between BMI and cardiometabolic risks, differs markedly between ethnic groups. Several studies have found that population specific BMI references and cut-offs are superior in detecting excess fat or cardiometabolic risks than universal BMI criteria. Therefore, the application of population specific references and cut-offs, such as those described in this thesis, likely optimises the overall sensitivity in detecting excess fat and cardiometabolic risks.
Undernutrition and cardiometabolic risks

The relation between overnutrition, expressed in adiposity, and cardiovascular and metabolic risks has been well established. Paradoxically, undernutrition in early childhood, usually expressed in a low birth weight, is also associated with increased (future) cardiometabolic risks. To explain this association several hypotheses have been proposed of which the ‘thrifty’ phenotype hypothesis or ‘foetal origins hypothesis’, has been studied extensively. It postulates that under- or malnutrition during the foetal development ‘reprograms’ the body’s glucose-insulin axis as an adaptation to nutritional scarcity, which ultimately leads to an increased risk of cardiometabolic diseases. The most compelling evidence supporting this hypothesis comes from studies of the ‘Dutch famine’ (or ‘Hunger winter’, 1944-1945) during the 2nd World War, which found that prenatal exposure to famine was related to a higher risk of cardiovascular disease and insulin resistance later in life compared with unexposed subjects. Similar results were found in a follow-up study of adults that during pregnancy or early childhood were exposed to the Biafran famine in Nigeria (1967-1970).34

Is low birth weight the expression of undernutrition?

Though the association between a low birth weight, as a proxy for intrauterine undernutrition, and subsequent disease was confirmed repeatedly, low birth weight remains a surrogate measure of fatness and does not distinguish the truly undernourished from well nourished but lean babies. Therefore, it remains unsure if these studies’ subjects were truly undernourished.35

* Thrifty means several things: in the context of the ‘thrifty phenotype hypothesis’ synonyms like economical, sparing, provident and preserving apply.
As we also showed in this thesis, low birth weight (<2500 g) is highly prevalent in South Asian children living in the Netherlands but it is unlikely that these babies are truly undernourished. South Asian neonates living in India were also shown to have a considerably lower mean birth weight than UK babies but they were not undernourished, as indicated by a generally normal subcutaneous fat mass but simultaneously a smaller lean body mass. Nevertheless, the relation between a low birth weight and insulin resistance has also been shown in Asian Indian neonates and older children. Compared with UK babies (generally lighter) Asian Indian babies were found to be hyperinsulinemic (a high insulin concentration in the blood). It may well be that these children remain more prone to hyperinsulemia or insulin resistance. Follow-up of a cohort of children in India showed that those born with a low birth weight were more insulin resistant at age 4 years and 8 years of age than children born with a higher birth weight.

In conclusion, South Asian babies are generally lighter at birth, but most are not undernourished. Though an increased risk of cardiometabolic disease in South Asians is already present at a young age, a direct relation with undernutrition seems unlikely.

Is low birth weight the expression of fat mass or fat-free mass?

Most research of the ‘thrifty phenotype hypothesis’ focussed on the fat mass, but there is also evidence supporting a relation to the fat-free or muscle mass. Several studies found that birth weight or birth weight-for-gestational-age is related to fat-free mass and not fat mass, a relationship that even extends into older age. Moreover, the amount of postnatal muscle mass has been shown to be highly influenced by genetic factors, accounting for 50 to 80 percent of the variability. Therefore, a neonate’s birth weight is likely more the reflection of (genetically determined) muscle mass than of fat mass.

How is the muscle mass related to insulin resistance?

One of the functions of the hormone insulin is to regulate the glucose (energy) delivery to the body’s cells, for which it primarily interacts with muscle cells. When these cells become less sensitive to insulin - a state called insulin resistance - the body’s feedback mechanism increases the insulin production in an attempt to restore the glucose transport into the cells. It is plausible that, since skeletal muscle is the primary target of insulin action, a smaller muscle mass itself may already lead to insulin resistance, as there are simply less points of interaction (receptors). This mechanism may be supported by studies showing an association between a low muscle mass and reduced insulin sensitivity, independent of the fat mass. Therefore, the association between birth weight and insulin resistance is likely moderated by the muscle mass.

As also the amount of body fat has been shown to be a moderator of insulin resistance, showing higher prevalences of insulin resistance with increasing body fat or BMI/weight both in neonates and adults, the glucose-insulin axis is most likely moderated both by muscle and fat mass. Subjects with a low birth weight or born small-for-gestational-age, who subsequently showed ‘catch-up growth’ in weight or BMI (likely because of fat deposition), were shown to be the most at risk for developing cardiometabolic diseases. The most insulin resistant Asian Indian babies were those born large (>3500 g). Although not known, these large babies may...
have actually had a small muscle mass but a large fat mass. Insulin resistance in 8-year old Asian Indian children was also highly prevalent in those born with a low birth weight but that had gained a large fat mass. It is likely that a large fat mass ultimately determines if cardiometabolic diseases develop in individuals with a low muscle mass.

In conclusion, we hypothesize that, independent of undernutrition or low birth weight, the amount of muscle and fat in relation to the body size moderates the subsequent risk of cardiovascular disease and type 2 diabetes. Those with a low muscle mass but a large fat mass are then likely to suffer the highest risk for developing cardiometabolic diseases.

*Why are South Asians predisposed to develop a small muscle mass?*

Both the ‘thrifty phenotype hypothesis’ and the ‘thrifty genotype hypothesis’, postulate that insulin resistance could have been advantageous in times of starvation.

A study of fetal undernutrition in sheep showed that in the sheep’s offspring the density of insulin-sensitive muscle cells was reduced. It is plausible that similar mechanisms are also active in humans, leading to the development of a lower muscle mass in undernourished fetuses, and consequently to a predisposition to insulin resistance. The underlying mechanism is called ‘programming’ or ‘developmental plasticity’ by which fetal development and metabolism is constantly adapted to environmental changes. There are several mechanisms by which an organism is programmed through environmental cues. For instance, the fetus’ gene expression may be changed by epigenetic alterations of the DNA, and also the tissue differentiation may be influenced in response to the environmental circumstances. With the ability of epigenetic changes to be imprinted in the DNA, the changes in the gene expression may become hereditary.

Where programming during early development is usually a short term adaptation to an unexpected environment, natural selection of specific genes that are advantageous during prolonged periods of low energy availability provide a more sustainable adaptation. India has been an agricultural society since 9,000 BC. A vegetarian diet, that is usually less energy dense, has been the predominant diet in South Asia for millennia. For that reason, the population has always been highly dependent on the crop yields to be able to feed the population. Droughts and policy mismanagement have frequently lead to crop failures, and consequently to frequent periods of famine. The past 2,500 years at least 90 famines were recorded, but the true number is likely to be much higher. Especially during the 18th and 19th century, famines have had devastating societal consequences, with an estimated total death count of 60 million people. These conditions may have been the trigger to a natural selection of those best adapted to nutritional deprivation, leading to the development of a ‘thrifty genotype’. One of the thrifty adaptations to nutritional scarcity that may have evolved in South Asian populations is the generally smaller muscle mass. Since a smaller muscle mass is associated with a lower basal metabolic rate, it automatically lowers the energetic demand of the body.

In conclusion, evidence is increasing that in the relation between birth weight and the risk of cardiometabolic diseases both environmental and genetic factors play a role. However, in the case of South Asians, the typical thin-fat body composition and as a consequence the extremely
high risk of developing cardiometabolic diseases, has been more likely naturally selected in the population as a long term thrifty adaptation to nutritional deprivation. The conceptual model in figure 2 shows the hypothesised relationship between a low birth weight and cardiometabolic disease risks.

**Figure 2** Conceptual model of the association between birth weight and cardiometabolic risks

**8.3 IMPLICATIONS**

*Health care professionals*

With the current universal child growth standards health risks in South Asian children are inadequately detected. Underweight or thinness are overestimated while overweight and obesity are underestimated. Both the overestimation of thinness and underestimation of overweight may add to the development of cardiovascular disease and type 2 diabetes mellitus.
Catch-up growth of thin infants has been repeatedly shown, both in Asian Indians and in other ethnic groups, to increase the risk of cardiometabolic disease.\textsuperscript{37,51,62} However, parents of thin children are often advised to have their children gain weight, which in turn will lead to the development of fat in stead of muscle, and consequently to increased cardiometabolic risks. On the other hand, South Asian children at risk for developing cardiometabolic diseases (with a large fat mass but a small muscle mass) are not adequately detected with current universal screening methods, resulting in preventive measures and interventions to start late or not at all. The application of the BMI cut-offs presented in this thesis likely lead to less misclassifications of the nutritional status and may therefore aid in the prevention of cardiovascular diseases and diabetes mellitus type 2. Furthermore, the use of ethnic specific BMI criteria in clinical practice may lead to parents becoming more aware of what is considered a healthy weight or BMI for their child at an earlier stage.

Although South Asian children in the Netherlands were on average shorter than Dutch children, the use of the current Dutch height reference charts may be sufficient for assessing the height of South Asian children, except during the first 6 months after birth and during adolescence. In boys between the age of 6 months and 14 years and in girls between 6 months and 12 years the difference in length/height with Dutch children remained fairly stable at the -0.5 SD level, indicating similar growth patterns. Also for Turkish and Moroccan children in the Netherlands youth health care professionals are recommended to use the height-for-age charts of Dutch children and switch to the ethnic specific height-for-age charts if in doubt, for instance if the height deviates from the child's own growth channel (the relative distance from the SD-lines).\textsuperscript{63} As the differences in height between South Asian children and Dutch children increase during adolescence, the application of ethnic specific charts during this period may aid in the proper assessment of height.

\textit{Policy makers}

Commonly, underweight prevalence rates follow a country's socioeconomic development. In the case of India this rule does not seem to apply, a paradox called the ‘Asian enigma’.\textsuperscript{64} While India's economic growth is greater and poverty levels are lower than in many other developing countries, the undernutrition rates (based on universal criteria) have only slightly changed in the past decades.\textsuperscript{65} Still, India has the highest childhood underweight rates in the world.\textsuperscript{66} Even though it is known that the body composition of South Asians differs from other ethnic groups,\textsuperscript{5,6,20} the high thinness rates are mostly related to pathology, in most cases to malnutrition and undernutrition.\textsuperscript{65,67} Nevertheless, current evidence indicates that most thin South Asian children, as indicated by a low BMI, are not undernourished at all, as a normal or even high fat mass is found in these children.\textsuperscript{6,68} In addition, we showed that even healthy affluent South Asian children living in a western country have high levels of thinness (based on universal BMI criteria). This suggests that ethnic specific weight and BMI criteria are needed to be able to properly assess the nutritional status of South Asian children. Application of South Asian specific growth standards will likely solve this ‘Asian enigma’.
The support of South Asian governments and organisations like WHO and Unicef for implementing such standards may likely result in an improvement of the future health of South Asian populations. Although the height references and BMI cut-offs presented in this thesis have not been validated with actual health outcomes, and the suitability for other South Asian populations has not been tested, these may provide a better tool for assessing the nutritional status of this ethnic group than the current universal height references and BMI criteria.

8.4 CONCLUSIONS AND DIRECTIONS FOR FUTURE RESEARCH

The epidemiological studies of this thesis generally support the hypothesis that also in a developed country as the Netherlands South Asian children are predisposed to a lower weight and BMI. Furthermore, these studies also suggest that current universal criteria to assess a child’s nutritional status are unsuitable for South Asian populations. To be able to better assess the nutritional status and height development we developed height-for-age references and BMI cut-offs, based on measurements of South Asian children living in the Netherlands.

As the studies of this thesis were restricted to South Asian children in the Netherlands, the results cannot directly be generalised to South Asian populations in other countries, even though the developed height-for-age and BMI-for-age charts were highly compatible to current Asian Indian charts. Therefore, further research is needed to confirm that length/height, especially length during infancy, and body composition in South Asian populations in other countries are similar to South Asian children in the Netherlands.

Furthermore, as the BMI cut-offs of this thesis were statistically derived, the second step is to validate these BMI criteria with actual body composition data and (cardiometabolic) health outcomes, such as blood pressure, blood lipids, and insulin resistance.

As we hypothesized that the actual muscle mass and fat mass may be moderators in the relation between (birth) weight/BMI and the subsequent health risks, it is also recommended to study the cardiometabolic risk profiles in relation to direct measures of body composition (muscle mass and fat mass) instead of surrogate measures such as weight and BMI. Such studies might provide new insights into the causal pathway leading to the development of cardiometabolic diseases.

REFERENCES


