Obesity and metabolic syndrome: from clinical to public health perspectives: results from population-based studies of the Dutch and Indonesian populations

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Chapter 7

Summary and General Discussion

This thesis was aimed to provide deeper insight into clinical and public health aspects of obesity and metabolic syndrome. In detail, we (1) investigated the sex-specific relations of abnormal body fat distribution with the occurrence of cardiometabolic diseases, (2) examined how ethnic differences in adiposity contribute to the different cardiometabolic risks between ethnic populations, and (3) identified patients' perceptions and population characteristics that may contribute to a better (self-) management of obesity and metabolic syndrome. In this chapter, we provide an overview of our main observations, the interpretations and potential implications, the strengths and limitations of our research, and future research perspectives.

Summary of Main Findings

In **Part I (Chapter 2)** of this thesis, we investigated sex-specific associations of excess visceral fat and excess liver fat with the incidence of type 2 diabetes and cardiovascular diseases in middle-aged men and women in ten years of follow-up. Our results show that both visceral and liver fat were associated with an increased risk of type 2 diabetes. However, we could not detect associations with cardiovascular diseases. Compared with individuals with low visceral fat and low liver fat, those with both high visceral and high liver fat had a four-fold increased risk of type 2 diabetes. The relative contributions of visceral fat and liver fat to the incidence of type 2 diabetes were relatively similar in men, whereas in women visceral fat in particular increased the risk of type 2 diabetes.

In **Part II** of this thesis, we investigated the different risks and burdens of obesity and metabolic syndrome in populations with different ethnicities. In **Chapter 3**, we investigated whether body fat distribution, represented as overall and abdominal obesity, were differentially associated with the risk of metabolic syndrome in Asian-Indonesian and Caucasian-Dutch populations. The prevalence of metabolic syndrome was higher in the Asian-Indonesian population (39%) than in the Dutch population (29%). More Indonesian women than men had metabolic syndrome, whereas the opposite was true for the Dutch population. We observed that abdominal obesity was more strongly related to metabolic syndrome than overall obesity in both populations. Nevertheless, when considering the associations with the separate components of metabolic syndrome, an exception existed for hypertension, being a component that was more driven by overall obesity rather than abdominal obesity, particularly in the Dutch population. Whereas the relative contributions of all components were similar in Indonesian men, Indonesian women, and Dutch men, in Dutch women the risk of metabolic syndrome was primarily explained by the increased risks of hypertriglyceridemia and low HDL-cholesterol in relation to abdominal obesity. In this study, we did not find evidence that abdominal obesity was more strongly associated with metabolic syndrome in the Asian-Indonesian population than the Caucasian-Dutch population.

In **Chapter 4**, we examined the ethnic variations in the serum concentrations of leptin and adiponectin, the two major adipocyte-derived hormones, and how the two hormones

relate to the risk of metabolic syndrome in the Asian-Indonesian and Caucasian-Dutch populations. For this, we analysed the data from the NEO and SUGARSPIN studies to represent the two populations with different ethnicities. We observed that although in the total population leptin concentrations were lower in the Asian-Indonesian population, within the same BMI the leptin levels were similar in the two populations. This suggests that leptin production per gram of adipose tissue is similar in the two populations, and therefore a similar metabolic activity of adipose tissue with regard to leptin. In contrast, adiponectin concentrations were consistently lower in the Indonesian population, both in the general population and within the same BMI. Nevertheless, despite these differences in leptin and adiponectin, the two hormones were not related to the risk of metabolic syndrome in the total Asian-Indonesian population. Also within the same BMI category, we did not find evidence that the associations of leptin and adiponectin with the metabolic syndrome were stronger in the Asian-Indonesian than the Caucasian-Dutch population, and thus these two hormones could not explain the increased cardiometabolic risks of Asians compared with Westerns. It must be noted that total body fat strongly influenced the associations of leptin and adiponectin with the metabolic syndrome. In the Indonesian population, all associations disappeared after additional adjustment for total body fat, which indicates no effect of the two hormones beyond the effect of total body fat on the metabolic syndrome.

In addition to exploring the aetiologic pathways in obesity and metabolic syndrome, in **Part III** of this thesis, we identified patients' perceptions and population characteristics that may contribute to a better (self-)management of obesity and metabolic syndrome. In **Chapter 5**, we investigated illness perceptions in individuals with overweight and obesity in the NEO study, and how the perceptions were associated with health-related quality of life. We observed that compared with those without obesity, individuals with obesity perceived their conditions to be 'threatening', as reflected by stronger negative illness perceptions. However, this perception was less pronounced in individuals with abdominal obesity than those with overall obesity, which implies less awareness of individuals with abdominal obesity regarding their condition and the negative consequence. Health-related quality of life was impaired in individuals with obesity, and the impairments were related to the negative illness perceptions in these individuals. The majority of individuals attributed their behaviour/lifestyle as the cause of obesity, implying the potential and importance of incorporating behaviour/lifestyle intervention in the management of obesity.

Finally, in **Chapter 6**, using large-scale data of the 2013 and 2018 Indonesian National Health Surveys, we investigated to what extent adherence to the national healthy lifestyle guideline; composed of physical activity, healthy diet, and refrain from smoking and alcohol; was associated with the risk of metabolic syndrome in the population. In addition, we explored how the associations differ between sex, age, urban/rural, and BMI categories. For example, in analysis categorised by sex, compared with men who did not adhere to the guideline, men who adhered had lower odds of metabolic syndrome. In addition, compared with young adults (<45 years) who did not adhere, middle-aged (45-65 years) who adhered to the guideline had lower odds of metabolic syndrome. In categorisation by urban/rural, compared with urban individuals who did not adhere to the guideline, urban individuals who adhered had lower odds of metabolic syndrome. In all BMI categories, particularly in the overweight and obesity categories, those who adhered to the guideline had lower odds of metabolic syndrome than those who did not. We also observed that women, urban populations, and those with higher BMI all had increased prevalence odds ratios of metabolic syndrome compared with the specific reference group in each categorisation. In conclusion, adherence to the national guideline may confer cardiometabolic health benefits to men, the middle-aged, urban population, and those with overweight and obesity.

Interpretations and Potential Clinical and Public Health Implications

In **Chapter 3**, we show that 90% of the Asian-Indonesian population and 81% of the Caucasian-Dutch population had at least one component of metabolic syndrome. This reveals the urgent need for effective public health policies to prevent and control the impending global burden of metabolic syndrome. Taken everything together, there are several potential practical implications from the findings of this thesis.

First, findings from **Chapters 3 and 4** imply that differences in abdominal obesity (waist circumference) and serum leptin and adiponectin concentrations could not explain the increased cardiometabolic risks of the Asians compared with Western populations. In these chapters, we did not find evidence that the associations of waist circumference with metabolic syndrome, as well as the associations of leptin and adiponectin with the metabolic syndrome, were stronger in the Asian-Indonesian than the Caucasian-Dutch population. Thus, other pathways than these associations should be explored to explain the increased cardiometabolic risks of the Asian population at the same BMI.

Second, this thesis highlights the importance of focusing on **abdominal obesity** to reduce the cardiometabolic burden of the global population. In **Chapter 3,** we show that abdominal obesity was more strongly related to the risk of metabolic syndrome than overall obesity in both the Asian-Indonesian and the Caucasian-Dutch populations. Previous studies have shown that excess visceral fat is the driver of the increased cardiometabolic risks associated with abdominal obesity (1–4). In **Chapter 2**, we additionally showed that both isolated and joint excess visceral fat and excess liver fat were associated with an increased risk of type 2 diabetes. This finding suggests that measuring visceral fat and liver fat content is essential for determining cardiometabolic disease risk stratification and directing prevention and treatment strategies. If the measurement of visceral and liver fat by MRI is not practical due to cost or logistic concerns in the developing countries (which comprise most of the Asian population) (5), routine measurement of waist circumference

or non-invasive indices such as the hypertriglyceridemic waist can be a relatively reliable and affordable alternative (2,6,7). Nevertheless, despite the negative health impacts of abdominal obesity, the general public appeared to be less aware of abdominal obesity than overall obesity (**Chapter 5**). This finding suggests that despite being commonly discussed in medical fields, 'abdominal obesity' may not translate into a tangible, perceptible phenomenon for the average person. When unmeasured and undiscussed, patients may not be aware that they have abdominal obesity and the health risks that pertain to it. This may impose a serious health problem, as patients may be less inclined to take proper (self-)management if they do not perceive the threat (8–11). This implies that raising public awareness of abdominal obesity and its negative effect should be a central agenda for healthcare providers.

Third, this thesis highlights the importance of incorporating non-medical interventions in managing obesity and metabolic syndrome. For example, behaviour/lifestyle interventions or modification programs have ample potential to be well-received by the general population, as the majority of individuals with obesity attributed their behaviour as the cause of their condition, and studies have shown that these individuals are likely to accept behavioural interventions (12,13). Additionally, as those with negative illness perceptions tend to adapt a maladaptive coping behaviour (10), psychosocial intervention to modify the negative perceptions into more positive ones in individuals with obesity may also help patients engage in adaptive, proper self-management. Improvement in the perceptions may also lead to a better health-related quality of life in individuals with obesity, as we observed in **Chapter 5**.

Finally, we observed that sociodemographic differences, including sex-, age, and urban/rural characteristics, should be taken into account when designing public health policies to achieve the most optimal benefit for the general population. In particular, this thesis emphasises the sex differences in the associations of fat depots with cardiometabolic outcomes in men and women, which may in part explain the different cardiometabolic risks between sexes. For example, in **Chapter 2,** we observed that visceral fat in particular increased the risk of type 2 diabetes in women, and thus the importance to prevent or reduce visceral fat in women is paramount. In **Chapter 3,** we observed that abdominal obesity was more strongly associated with metabolic syndrome in Dutch women than men. In the Asian-Indonesian population, women had a higher prevalence of obesity and metabolic syndrome than men (**Chapter 3** and **4**). In **Chapter 6,** our results imply that more is needed than just living a healthy lifestyle for women, and group-specific targeted interventions such as early screening and prevention programs will potentially be beneficial in reducing the burden of obesity and metabolic syndrome in this group.

Strengths and Limitations of the Studies

The main strength of the studies we have performed is the large population size, derived from the NEO study (14), the SUGARSPIN study (15), and the 2013 and 2018 Indonesian Health Surveys (16,17). With this large sample size, we were able to generalise the results to the broader Asian-Indonesian and Western-Dutch populations. This also enabled us to conduct many subgroup analyses in our studies.

However, several limitations should be noted, which in general can be grouped into limitations by study designs and measurements.

Limitation by study designs

All studies that construct this thesis were observational, and therefore may suffer from residual confounding by unknown, unmeasured, or inaccurately measured confounding. Four out of five studies in this thesis were cross-sectional by design, and thus may suffer from reverse causation. Nevertheless, in our opinion, a true randomised clinical trial is not feasible, considering obesity and ethnicity are not factors that can be randomised. Furthermore, in **Chapter 5**, the absence of longitudinal data hindered us from assessing whether the negative illness perceptions and the consequently impaired health-related quality of life in individuals with obesity persisted or changed over time, whereas theoretical studies proposed that illness perceptions are dynamics as the individuals constantly appraise them and may change over time (8–11).

Limitation by study measurements

In **Chapter 2**, as we only used the preliminary follow-up data of the NEO study with incomplete inclusions of cardiovascular diseases (CVD), it remains unclear whether the absence of association between visceral or liver fat and CVD was due to the underestimation of the true incidence rates of CVD and the insufficient power to detect the risks. Therefore, future studies with the final follow up data with longer follow-up and complete inclusions of CVD (including hospital diagnoses) are needed to confirm our results on CVD.

Next, although the NEO study that represented the Western-Dutch population in this thesis had multiple advanced phenotyping measurements of obesity, the studies that represent the Asian-Indonesian population were much larger in sample size, and therefore invasive measurements were not feasible. Probably the most crucial unavailable measurement is the direct assessment of visceral fat in the Asian-Indonesian population. As a result, in **Chapter 3**, we could only use abdominal obesity as a proxy of visceral obesity, measured by waist circumference. In addition, information on lipid-lowering medication use was not obtained from the participants in the Asian-Indonesian population, whereas this is a crucial variable in diagnosing dyslipidemia. This may result in an underestimation of the prevalence of hypertriglyceridemia and low HDL-cholesterol in the Indonesian

population. Nevertheless, as lipid-lowering medications are not routinely prescribed in Indonesia (18), we expect that this potential underestimation would not have influenced our results.

For **Chapters 3** and **4**, the leptin and adiponectin concentrations were measured using different methods in the Asian-Indonesian and Caucasian-Dutch populations (ELISA vs RadioImmunoAssay techniques). Blood glucose was also measured differently, with a rapid fingertip capillary glucometer in the Indonesian population, versus a standard clinical chemistry analysis of venous plasma sample in the Dutch population, which may result in a possible overestimation of hyperglycemia in the Indonesian population (19). However, previous studies have shown that mean differences between measurements using ELISA and RadioImmunoAssay techniques (20,21), and between point-of-care glucose testing and standard laboratory test (22–25), were relatively minor. Therefore, the measurements of the two studies were still clinically comparable and would not change our study conclusions. Nevertheless, despite comparable measurements, we acknowledged that the two different ethnic populations differed in many cultural, biopsychosocial, and environmental aspects. This should be taken into account when 'comparing' the results from the two populations.

Furthermore, pertaining to the data from the 2013 and 2018 Indonesian National Health Surveys **(Chapter 3 and 6)**, as the nature of data collection on lifestyle information in these surveys was via an interviewer-assisted questionnaire, it is possible that participants may have provided socially desirable answers to the questions. This might have led to more people seeming to adhere to the guideline while they actually did not, and thus consequentially underestimating the relation between the lifestyle factors and the risk of metabolic syndrome. Nevertheless, despite the measurement limitations of the surveys, the Indonesian National Health Survey is the largest and best available health data representing the Asian-Indonesian population, and thus the limitations should not outweigh the importance to report the study observations.

External Validity

As we used various data from multiple populations, the external validity of our studies is different between chapters. For example, as **Chapters 2** and **5** were conducted in a population with a majority (95%) of White-Caucasian ethnicity, results from these studies may be more applicable to other Western/European populations, and results need to be confirmed in other ethnicities. In addition, in **Chapter 2,** only those without MRI contraindications were included (body circumference ≥170 cm, implanted metallic devices, or claustrophobia), and thus the results may only apply to those eligible for MRI.

In **Chapters 3, 4,** and **6**, as we used large-scale and nationally representative data from the Indonesian population, results from our studies can be generalised to the whole Asian-Indonesian population, and potentially the neighbouring populations in Southeast Asian countries who have similar sociodemographic characteristics. However, Asia is the largest continent and home to approximately 60% of the world's population, and whether results from our studies applied to the whole Asian population remained to be investigated. Nevertheless, as most studies investigating obesity and metabolic syndrome in Asia were done in populations with either Chinese or Indian backgrounds (26–33), our results add to the literature in providing results from the Southeast Asian population.

In **Chapter 4**, the SUGARSPIN study represents an Indonesian population living in rural areas, hence results from this chapter may need to be confirmed in the urban Indonesian population. However, a previous study had observed that adiponectin concentrations were not different between urban and rural Indonesians (34), which may support the generalizability of our results to the greater Indonesian population.

Future Research Perspectives

Addressing the limitations and implications of our study, we recommend future studies to adapt the following perspectives:

First, as we observed sex differences in the associations of fat depots with cardiometabolic outcomes in men and women, future studies are needed to confirm whether these fat depots are more crucial underlying risk factors in one sex than the other. In particular, as implied in **Chapters 2 and 3,** future studies to unravel the underlying mechanisms of the detrimental metabolic effects of visceral fat in women are necessary. These studies will help explain the causes of the different cardiometabolic risks between sexes, and whether a sex-specific targeted intervention is necessary.

Second, we encourage future studies to use a direct measurement of visceral fat in the Asian population to investigate their cardiometabolic risks. The adipose tissue overflow hypothesis proposes that the Asian population has a smaller subcutaneous fat compartment than the Westerns, so that the lipids overflow to and accumulate earlier in the visceral fat compartment, resulting in the early development of cardiometabolic complications (35). In **Chapter 3**, we used abdominal obesity as a proxy of visceral obesity, and we did not find evidence that abdominal obesity was more strongly associated with metabolic syndrome in the Asian-Indonesian than the Caucasian-Dutch population. Although measurement error could contribute to this finding (36,37), it could also be because abdominal obesity is not accurately representing the amount of visceral fat. Thus, investigating the direct relation of the amount of visceral fat with the risks of metabolic syndrome in the Asian populations may provide a more definitive answer.

Third, we recommend that future studies use more direct clinical outcomes, such as the incidence of type 2 diabetes and cardiovascular diseases, or other pathways than metabolic syndrome in investigating the cardiometabolic risks. We chose metabolic syndrome as the outcome in the majority of our studies as it is a pathway from obesity complications that leads to cardiometabolic diseases (38–40). However, as we observed no associations between some of our study exposures (e.g., leptin and adiponectin) with the metabolic syndrome, whether these exposures associate directly with the occurrence

of cardiometabolic diseases or via other pathways than metabolic syndrome remained to be investigated.

Fourth, other biomarkers of total and abdominal body fat, besides leptin and adiponectin, and their relation to cardiometabolic health in the Asian population should be investigated. For example, as previous studies have shown that CD-14 and IL-18 are over-expressed in the circumstance of persistent low-grade systemic inflammation in omental adipose tissue (41), further studies on these two biomarkers are crucial. Additionally, although results from **Chapter 4** were consistent with Mendelian randomisation (MR) studies that show no causal association of adiponectin to type 2 diabetes and glucose homeostasis (42), it remained unclear why leptin was not related to metabolic syndrome in the Asian-Indonesian population. MR studies in a majority of White/European population have shown the causality of leptin to insulin resistance and hypertension (43,44), which were aligned to our findings in the Caucasian-Dutch population. Therefore, to provide a more definitive answer, GWAS and MR studies in the Asian population are needed to determine the causality of leptin, and possibly other biomarkers of adipose tissue, in relation to cardiometabolic health.

Fifth, in this thesis, we emphasise that obesity is not only a medical problem, but also a psychosocial issue (45). **Chapter 5** reveals a need for psychosocial intervention studies to improve the negative illness perceptions in individuals with obesity, and investigate whether this improvement translates into a more improved clinical outcome (e.g., weight loss) besides the health-related quality of life. Longitudinal studies examining illness perceptions, which should include non-white populations, are also needed to obtain a more crystal-clear answer on whether the negative perceptions in individuals with obesity persist or change over time.

Sixth, as we could only perform a cross-sectional study investigating the association between lifestyle and metabolic syndrome, future longitudinal studies are needed to see how individual changes in lifestyle relate to the risk of metabolic syndrome. In **Chapter 6,** we evaluated the national healthy lifestyle guideline from the government of Indonesia, and our findings put forward a concrete suggestion to help achieve a greater health benefit for the whole population. As this was the first study evaluating the guideline in relation to cardiometabolic health of the population, we recommend that this study can be a starting point for guideline evaluation in future studies.

Conclusions

In this thesis, we provided a deeper insight into the clinical and public health aspects of obesity and metabolic syndrome. We showed that the combination of both excess visceral fat and excess liver fat was associated with a four-fold increased risk of type 2 diabetes, and that in women, visceral fat in particular increased the risk of type 2 diabetes. Abdominal adiposity was more strongly associated with metabolic syndrome than overall adiposity in both the Asian-Indonesian and Western-Dutch populations. Despite lower adiponectin levels in the Asian-Indonesian population, adiponectin was not related to the metabolic syndrome in the Indonesian population and can not explain their increased cardiometabolic risk at the same BMI compared with the Western-Dutch population. Individuals with obesity perceived their conditions as 'threatening', but this perception was less pronounced in individuals with abdominal obesity than those with overall obesity. Adherence to the Indonesian national healthy lifestyle guideline may confer cardiometabolic health benefits to several groups of the population, particularly men, the middle-aged, urban population, and those with overweight and obesity.

Taken everything together, we highlighted the importance of abdominal obesity in the development of cardiometabolic complications. Nevertheless, despite being commonly discussed in medical fields, the general public appeared to be less aware of the meaning of 'abdominal obesity', and thus raising public awareness of abdominal obesity and its negative health impacts should be a central agenda. In addition, approaches based on sex differences and other sociodemographic characteristics, as well as non-medical interventions (e.g., behavioural or psychosocial), should be incorporated in public health strategies to manage obesity and metabolic syndrome. Finally, further studies to explain the increased cardiometabolic risks of the Asian population are needed to help reduce the high burden of morbidity and mortality of cardiometabolic diseases in these countries (46–49).

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