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

Sigit, F.S.

Chapter 1

General Introduction

General Introduction and Aims: Obesity as a Global Health Problem

Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health (1). The World Health Organization defines obesity based on the body mass index (BMI), which is a measure of a person's body weight in kilogram, divided by the square of his height in meters (kg/m^2) (2). For the western-adult population, overweight is defined as BMI $\geq$25 kg/m^2; and obesity as BMI $\geq$30 kg/m^2. It is estimated that 13%, or approximately 650 million, of the adult population worldwide have obesity. This estimate is predicted to escalate rapidly, as 39% of adults, or approximately 1.9 billion, have overweight. The prevalence of obesity is increased threefold from 1975 to 2016, with a faster-growing pace in low- and middle-income countries than high-income countries (1).

In this thesis, the overall aim is to provide insight into clinical and public health issues related to obesity. In detail, we will answer the following objectives:

1. to better understand the sex-specific relations of abnormal body fat distribution with cardiometabolic outcomes;
2. to investigate how ethnic differences in adiposity contribute to different cardiometabolic burdens in different ethnic populations; and
3. to identify patients' perceptions and population-specific characteristics that may contribute to the best attainable, patient-engaged, management of obesity and metabolic syndrome.

PART I. From abnormal body fat distribution to cardiometabolic outcomes: The pathophysiology.

Although the BMI classification is the most commonly used criteria to define obesity, it has major drawbacks: BMI cannot distinguish body composition, as it cannot differentiate body fat from muscle mass (3). Also, BMI cannot detect where in the body the accumulation of adipose tissue is located, whereas many studies have established that not only the excess fat mass matters in obesity, but also the abnormal body fat distribution (4–7). In particular, fat that is deposited in the abdominal region has the most detrimental health effects (8,9), and thus specific attention must be given to combat abdominal obesity, with or without the presence of overall obesity.

When the body is in a positive energy balance state, commonly due to excess calorie intake and low energy expenditure due to physical inactivity, the excess energy is stored and reserved as body fat (10,11). Based on the adipose tissue overflow hypothesis (12), excess fat is physiologically stored in the subcutaneous compartment, which is located directly beneath the skin (5,6). In circumstances that excess fat continuously accumulates, the fat fulfils the subcutaneous compartment to its maximum capacity and its plasticity becomes exhausted, and extra lipids may overflow to the intra-abdominal visceral

1
2
3
4
5
6
7
8

compartment (12), or result in ectopic fat accumulation in which fat is deposited in normally lean organs (7), such as the liver or the heart. This abnormal body fat distribution, when fat is stored in the visceral compartment or deposited in otherwise lean organs, is a precursor of cardiometabolic diseases (4–7). In particular, excess visceral fat and liver fat are associated with detrimental health effects and increased risks of type 2 diabetes and cardiovascular diseases (6,7,12,13). Visceral fat has been positively linked to insulin secretion and resistance (9), and influxes of free fatty acids and glycerol to the liver, which leads to hepatic glucose dysregulation and raised production of triglyceride-rich circulating lipoproteins, promoting atherosclerosis (7). In addition, excess liver fat, commonly manifested as non-alcoholic fatty liver disease (NAFLD), disrupts hepatic metabolism in general and may develop into hepatic steatosis or even cirrhosis (13).

In previous analyses, we observed that different fat depots were differentially associated with cardiometabolic outcomes in men and women. For example, whereas in men abdominal subcutaneous fat and visceral fat were associated with insulin resistance to a similar extent, in women visceral fat in particular was associated with insulin resistance and insulin secretion (9). We also observed that visceral fat contributed beyond overall adiposity to subclinical atherosclerosis, and more particularly so in women than men (14). However, whether liver fat is differentially associated with cardiometabolic outcomes in men and women remains unclear. Furthermore, to what extent the co-existence of both excess visceral fat and liver fat may amplify the adverse health effect and accelerate the occurrence of cardiometabolic diseases is also unclear.

Therefore, this part of the thesis is aimed to unravel sex-specific associations between abnormal body fat distribution; represented as excess intra-abdominal visceral fat, liver fat, and the combined phenotype of both; with the risk of type 2 diabetes and cardiovascular diseases.

PART II. Ethnic Differences in Adiposity and Metabolic Syndrome

One pathway of obesity that leads to cardiometabolic diseases is via the metabolic syndrome, which is a cluster of cardiometabolic abnormalities that occur concomitantly (8,15,16). The abnormalities are abdominal obesity, hypertension, hyperglycaemia, hypertriglyceridemia, and low HDL cholesterol; and metabolic syndrome is diagnosed as having at least three out of these five conditions **[Table 1]** (8,15,16). Early detection and proper management of metabolic syndrome are of utmost importance, as it is a reversible and manageable condition (17), before it fully transforms into the occurrence of type 2 diabetes and cardiovascular diseases.

The burden of metabolic syndrome differs disproportionately between populations. For example, it is well-established that, at the same BMI, Asian populations have an increased risk of developing metabolic syndrome compared with Western populations (18). In fact, the World Health Organization has set lower cut-offs for both overall and abdominal obesity in Asian populations than in Western populations, due to their increased risks of developing type 2 diabetes and cardiovascular diseases at an earlier stage of obesity, or at a lower amount of adipose tissue, than the Westerns (12,15,19).

The adipose tissue overflow hypothesis proposes that Asians have a different body fat distribution than Westerns (12,20,21): in particular, they have a smaller subcutaneous fat compartment, so that in the development of obesity, the excess lipid flows to the visceral area earlier than in Westerns (12). This hypothetically leads to a relatively higher amount of visceral fat within the total mass of adiposity **[Figure 1]**.

Besides this difference in body fat distribution, several studies have also reported that on average Asian populations have a higher concentration of leptin, but a lower concentration of adiponectin than Western populations (23–25). Out of various adipocyte-derived hormones, leptin and adiponectin are the two primary hormones that play an essential role in glucose homeostasis, insulin sensitivity, lipid metabolism, and platelet function (26–31). Leptin is an inflammatory hormone that induces oxidative

Table 1. Components of the metabolic syndrome, as defined by the Joint Interim Statement criteria (15).

Component	Criteria
Abdominal Obesity	Waist circumference above ethnic-specific cut-off (≥90 cm in Asian men and ≥80 cm in Asian women; ≥102 cm in European men and ≥88 cm in European women)
Hypertension	Systolic blood pressure >130 and/or diastolic blood pressure >85 mmHg **OR** use of antihypertensive agent(s)
Hyperglycemia	Fasting glucose >5.6 mmol/L **OR** use of a glucose-lowering agent(s)
Hypertriglyceridemia	Triglyceride ≥1.7 mmol/L **OR** use of a lipid-lowering agent(s)
Low HDL-Cholesterol	HDL-Cholesterol <1.0 mmol/L in men or <1.3 mmol/L in women **OR** use of medication(s) for reduced-HDL

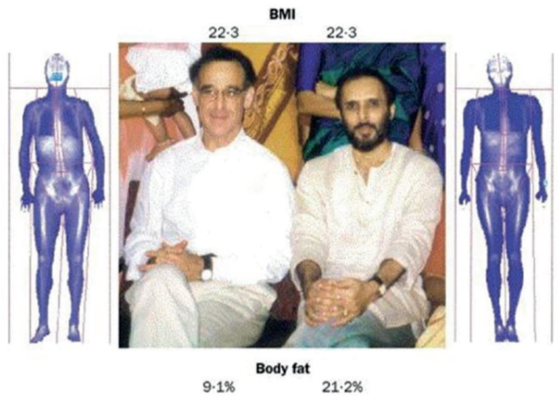

Figure 1. Illustration showing two men of Western and Asian descents. Both have the same BMI but a different amount of total body fat [Yajnik CS, Yudkin JS. Lancet 2004] (22).

stress in endothelial cells, stimulates the secretion of proinflammatory cytokines, and switches glucose metabolism to fatty acid oxidation (32–35). In contrast, adiponectin is the counteractive anti-inflammatory hormone that mediates protective effects with its insulin-sensitizing and anti-inflammatory properties (36,37). In obesity, leptin level increases whereas the adiponectin decreases (38,39), resulting in an imbalance that leads to impaired cardiometabolic function.

Nevertheless, studies are still needed to answer whether concentrations of leptin and adiponectin also differ between the Asian and Western populations at the same BMI, as this reflects the differences in hormonal/metabolic activities within the same amount of fat mass. Furthermore, whether the different secretions of these hormones relate to metabolic syndrome and can explain the increased cardiometabolic risks in the Asian population are also yet to be investigated.

Therefore, although it is well-established that Asians are more prone to develop cardiometabolic diseases (18,40–43), more evidence is needed to fully explain the still unclear mechanism that leads to the increased risks. In the second part of this thesis, we investigated the differences in adiposity and metabolic syndrome between Asian and Western populations. First, we investigated whether body fat distribution, represented as overall and abdominal obesity, in the two populations relates to a different risk of metabolic syndrome. Second, to examine the influence of adipocyte-derived hormones, we investigated the associations of leptin and adiponectin concentrations with the risk of metabolic syndrome in the two populations.

PART III. Patients' Perceptions and Public Health Aspects in the Management of Obesity

In the field of health psychology, the *Common Sense Model (CSM) of Illness Perception* proposes that when an individual experiences a health threat, which could be a deviation of bodily function or symptoms of a disease, the individual creates both cognitive and emotional 'perceptions' as a response to the health threat (44–47). These 'illness perceptions' then motivate the individual to choose/exhibit a coping response to address the health threat. The coping response will lead to an illness outcome, such as a recovery or persistent complaints, which the patients evaluate as meeting their expectations or not. The Common Sense Model proposes that the cycle of *illness perceptions → coping → illness outcomes* are cyclical. These processes form a continuous feedback loop, as the outcome evaluation helps them readjust their perceptions and coping if necessary, until the desired outcome is reached (44–47). In clinical practice, identifying how patients perceive their condition is crucial, as it may help support better engagement or adherence to the therapy (48,49), or explore the most well-suited individualised treatment choice.

The Common Sense Model implies that one must be aware of their condition first, before they can resort themselves to take action. In other words, when patients are less aware of their condition, they may be less inclined to take proper coping (44–47). For example, in the context of obesity, only patients that perceive their condition as threatening can consciously engage themselves in a weight loss intervention to improve their condition. However, with the multiple different definitions of obesity, such as overall obesity, abdominal obesity, and metabolically unhealthy obesity (50–53), it is unclear whether patients are aware of their conditions, how they perceive it, or whether these conditions are perceptible. For example, are patients aware of their abdominal obesity and its detrimental effects, when they have no overall obesity?

Finally, it is well-established that adopting a healthy lifestyle is a key factor in the management of obesity. In fact, many countries have now established healthy lifestyle guidelines as a behaviour intervention means for the general public (54). However, although it is known that lifestyle, including physical activity, healthy diet, and refrain from smoking and alcohol, is positively associated with general health (55–61), whereas it is also specifically related to the metabolic syndrome is yet unclear. Epidemiological studies observed conflicting results, as several studies showed negative associations between adopting a healthy lifestyle and the risk of metabolic syndrome (62,63), while other studies showed no association (64). This discrepancy may partly be due to diverse study designs and limited adjustment for confounding. Large population-based studies are therefore warranted to estimate the presence and strength of the association between adopting a healthy lifestyle with the risk of metabolic syndrome.

Therefore, in this part of the thesis, we analysed population-based data to help shape tailored therapy. First, in a population with oversampling of individuals with overweight and obesity (65), we investigated how the individuals perceive their condition, and how the perception relates to their health-related quality of life as an outcome. Second, using national health surveys data of a population (66,67), we investigated whether adherence to the national healthy lifestyle guideline may provide benefit to reduce the risk of metabolic syndrome, while also considering sociodemographic characteristics such as sex, age, and urban/rural living situation, as these factors are associated with the metabolic syndrome (68–79).

Outline of this Thesis

In the first part of this thesis (**Chapter 2**), we aimed to unravel sex-specific separate and joint associations of visceral fat and liver fat with the incidence of type 2 diabetes and cardiovascular diseases in middle-aged men and women in ten years of follow-up. In the second part of this thesis, we aimed to provide insight into why Asian populations develop metabolic complications at lower amounts of adiposity than Western populations. To that extent, we investigated the prevalence of metabolic syndrome and its components, and relations between overall and abdominal obesity with the risk of metabolic syndrome in an Asian-Indonesian and Caucasian-Dutch population **(Chapter 3)**. In addition, we investigated the differences in the secretion of adipocyte-derived hormones leptin and adiponectin, and how the hormones play a role in the different risks of metabolic syndrome in the two populations **(Chapter 4)**.

In the third part of this thesis, we investigated how individuals with overweight and obesity perceive their condition, and how these perceptions were associated with health-related quality of life (**Chapter 5)**. Additionally, we investigated whether adherence to a national healthy lifestyle guideline was associated with the risk of metabolic syndrome, and how the associations differed between age, sex, urban/rural, and BMI categories (**Chapter 6)**. Finally, a summary of all important findings in studies that construct this thesis, the implications, and future research directions are discussed in **Chapter 7**.

Study Designs and Populations Used in this Thesis

This thesis includes populations of different ethnic backgrounds from multiple studies. Four out of five articles in this thesis analysed the population of the Netherlands Epidemiology of Obesity (NEO) study (65), which represented the Caucasian-Dutch population discussed in this thesis. The Asian-Indonesian population investigated in this thesis is included from three different studies: the SUGAR Scientific Program Indonesia – Nederland (SUGARSPIN) study and the 2013 and 2018 Indonesian National Health Surveys (66,67,80).

The Netherlands Epidemiology of Obesity (NEO) Study

Data from the NEO study were analysed and presented in **Chapters 2, 3, 4, and 5.** The NEO study is a population-based prospective cohort study that aims to investigate pathways that lead to obesity-related diseases. The NEO study is conducted in Leiden (in the west of the Netherlands) and its surroundings, with oversampling of individuals with overweight or obesity (BMI>27kg/m^2). To correct for this oversampling, individuals from Leiderdorp, a neighbouring municipality, were invited to participate in the study regardless of their BMI (65).

The study recruitment was done via local advertisements and invitation letters to potential participants aged 45-65 from their general practitioners. The study includes 6,671 middle-aged adults, with the majority (95%) of participants are of white ethnicity. During the baseline measurement in 2008-2012, participants were invited to come to the study site at Leiden University Medical Center (LUMC) to undergo an extensive physical examination. Of the participants who were eligible for MRI, approximately 35% were randomly selected to undergo direct assessment of abdominal fat. In total, 2,580 participants had a valid measurement of visceral adipose tissue by MRI, and 2,083 participants of hepatic triglyceride content by ^{1}H-MRS.

Patients are followed for the incidence of cardiometabolic diseases, which are extracted from the electronic medical records at general practices (65). The medical ethical committee of LUMC had approved the design of the NEO study, and all participants had signed informed consent.

The SUGAR Scientific Programme Indonesia – Nederland (SUGARSPIN) Study

Population from the SUGARSPIN study is included in **Chapter 4.** SUGARSPIN Study is a double-blind, randomised clinical trial that aims to investigate the effect of parasitic infection on insulin resistance and cardiometabolic health. The SUGARSPIN study is conducted in Nangapanda, Flores (the South-Eastern part of Indonesia), in a population of a rural setting. All participants are of Malay-Austronesian descent. The study includes non-pregnant, adults aged≥16 years who were randomised at the household level. Details of the SUGARSPIN study design has been described elsewhere (80).

After randomisation, all participants were invited for a baseline visit at the study site. Participants were instructed to fast overnight prior to the blood sampling and fill in questionnaires to obtain information on demographics and lifestyles. The medical ethical committee of the Leiden University Medical Center and the University of Indonesia (ref: 549/H2.F1/ETIK/2013) had approved the SUGARSPIN study design. All participants had signed an informed consent form (80).

Chapter 4 of this thesis uses the baseline measurement data from the SUGARSPIN trial, before any interventions were conducted. Participants younger than 18 years were excluded.

The 2013 and 2018 Indonesian National Health Surveys

Data from the 2013 Indonesian National Health Survey were used in **Chapter 3 and Chapter 6,** whereas data from the 2018 survey were used in **Chapter 6.** The Indonesian National Health Surveys (Indonesian: *Riset Kesehatan Dasar; 'RISKESDAS')* is a periodic nationwide survey conducted every five years by the Ministry of Health, the Government of Indonesia, with the 2013 and 2018 surveys being the two most recent. The national survey is aimed to screen for the presence of infectious, cardiometabolic, and degenerative diseases, and to investigate the general health status of the citizens. Samples were obtained with a stratified, multi-stage, systematic random sampling and a probability proportional to size method to account for the differences in the geographical and urban/rural densities across the 34 provinces. Weighting factors were used in the analyses to ensure that the study sample represented the citizens of Indonesia nationally (66,67).

The 2013 survey sampled 1,027,763 participants of all ages, of which 34,274 were adults aged >15 years who were randomly sampled to undergo blood sampling and clinical laboratory tests. The 2018 survey population were 1,017,290 participants, of whom 33,786 were adults who were randomly sampled for the blood tests. All participants had agreed to participate and signed informed consent (66,67). In **Chapters 3** and **6** of this thesis, data from the subpopulation of the surveys who were non-pregnant, adult individuals, and who were randomly selected for blood glucose and lipid tests were used. The two chapters included in this thesis were approved by and registered in the National Institute of Health Research and Development, Ministry of Health, Republic of Indonesia (81).

References

1. World Health Organization. Obesity and overweight [Internet]. [cited 2021 Sep 9]. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
2. World Obesity Federation. Obesity Classification [Internet]. [cited 2021 Sep 10]. Available from: https://www.worldobesity.org/about/about-obesity/obesity-classification
3. Nuttall FQ. Body Mass Index: Obesity, BMI, and Health: A Critical Review. Nutr Today. 2015 May;50(3):117–28.
4. Després J-P, Lemieux I. Abdominal obesity and metabolic syndrome. Nature. 2006 Dec 14;444(7121):881-7.
5. Tchernof A, Després J-P. Pathophysiology of human visceral obesity: an update. Physiol Rev. 2013 Jan;93(1):359-404.
6. Neeland IJ, Ayers CR, Rohatgi AK, Turer AT, Berry JD, Das SR, et al. Associations of visceral and abdominal subcutaneous adipose tissue with markers of cardiac and metabolic risk in obese adults. Obesity (Silver Spring). 2013 Sep;21(9):E439-447.
7. Neeland IJ, Ross R, Després J-P, Matsuzawa Y, Yamashita S, Shai I, et al. Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: a position statement. Lancet Diabetes Endocrinol. 2019 Sep;7(9):715-25.
8. Internatonal Diabetes Federation. Consensus statements [Internet]. [cited 2021 Sep 9]. Available from: https://www.idf.org/e-library/consensus-statements/60-idfconsensus-worldwide-definitionof-the-metabolic-syndrome.html
9. de Mutsert R, Gast K, Widya R, de Koning E, Jazet I, Lamb H, et al. Associations of Abdominal Subcutaneous and Visceral Fat with Insulin Resistance and Secretion Differ Between Men and Women: The Netherlands Epidemiology of Obesity Study. Metab Syndr Relat Disord. 2018 Feb;16(1):54–63.
10. Hill JO, Wyatt HR, Peters JC. Energy balance and obesity. Circulation. 2012 Jul 3;126(1):126–32.
11. Hall KD, Heymsfield SB, Kemnitz JW, Klein S, Schoeller DA, Speakman JR. Energy balance and its components: implications for body weight regulation. The American Journal of Clinical Nutrition. 2012 Apr 1;95(4):989–94.
12. Sniderman AD, Bhopal R, Prabhakaran D, Sarrafzadegan N, Tchernof A. Why might South Asians be so susceptible to central obesity and its atherogenic consequences? The adipose tissue overflow hypothesis. International Journal of Epidemiology. 2007 Feb 1;36(1):220–5.
13. Eguchi Y, Eguchi T, Mizuta T, Ide Y, Yasutake T, Iwakiri R, et al. Visceral fat accumulation and insulin resistance are important factors in nonalcoholic fatty liver disease. J Gastroenterol. 2006 May;41(5):462–9.
14. Gast KB, den Heijer M, Smit JWA, Widya RL, Lamb HJ, de Roos A, et al. Individual contributions of visceral fat and total body fat to subclinical atherosclerosis: The NEO study. Atherosclerosis. 2015 Aug;241(2):547–54.
15. Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009 Oct 20;120(16):1640–5.
16. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005 Oct 25;112(17):2735–52.
17. Han TS, Lean ME. A clinical perspective of obesity, metabolic syndrome and cardiovascular disease. JRSM Cardiovascular Disease. 2016 Jan 1;5:2048004016633371.
18. Ranasinghe P, Mathangasinghe Y, Jayawardena R, Hills AP, Misra A. Prevalence and trends of metabolic syndrome among adults in the asia-pacific region: a systematic review. BMC Public Health. 2017 Jan 21;17(1):101.
19. Caprio S, Daniels SR, Drewnowski A, Kaufman FR, Palinkas LA, Rosenbloom AL, et al. Influence of Race, Ethnicity, and Culture on Childhood Obesity: Implications for Prevention and Treatment. Diabetes Care. 2008 Nov 1;31(11):2211.
20. Deurenberg P, Deurenberg-Yap M, Guricci S. Asians are different from Caucasians and from each other in their body mass index/body fat per cent relationship. Obes Rev. 2002 Aug;3(3):141–6.
21. Wang J, Thornton JC, Russell M, Burastero S, Heymsfield S, Pierson RNJ. Asians have lower body mass index (BMI) but higher percent body fat than do whites: comparisons of anthropometric measurements. Am J Clin Nutr. 1994 Jul;60(1):23–8.
22. Yajnik CS, Yudkin JS. The Y-Y paradox. Lancet. 2004 Jan 10;363(9403):163.
23. Conroy SM, Chai W, Lim U, Franke AA, Cooney RV, Maskarinec G. Leptin, adiponectin, and obesity among Caucasian and Asian women. Mediators Inflamm. 2011;2011:253580.
24. Mente A, Razak F, Blankenberg S, Vuksan V, Davis AD, Miller R, et al. Ethnic variation in adiponectin and leptin levels and their association with adiposity and insulin resistance. Diabetes Care. 2010 Jul;33(7):1629–34.
25. Rasmussen-Torvik LJ, Wassel CL, Ding J, Carr J, Cushman M, Jenny N, et al. Associations of body mass index and insulin resistance with leptin, adiponectin, and the leptin-to-adiponectin ratio across ethnic groups: the Multi-Ethnic Study of Atherosclerosis (MESA). Ann Epidemiol. 2012 Oct;22(10):705–9.
26. Al-Hamodi Z, Al-Habori M, Al-Meeri A, Saif-Ali R. Association of adipokines, leptin/adiponectin ratio and C-reactive protein with obesity and type 2 diabetes mellitus. Diabetol Metab Syndr. 2014;6(1):99.
27. Zhuo Q, Wang Z, Fu P, Piao J, Tian Y, Xu J, et al. Comparison of adiponectin, leptin and leptin to adiponectin ratio as diagnostic marker for metabolic syndrome in older adults of Chinese major cities. Diabetes Res Clin Pract. 2009 Apr;84(1):27–33.
28. López-Jaramillo P, Gómez-Arbeláez D, López-López J, López-López C, Martínez-Ortega J, Gómez-Rodríguez A, et al. The role of leptin/adiponectin ratio in metabolic syndrome and diabetes. Horm Mol Biol Clin Investig. 2014 Apr;18(1):37-45.
29. Donoso MA, Muñoz-Calvo MT, Barrios V, Martínez G, Hawkins F, Argente J. Increased leptin/adiponectin ratio and free leptin index are markers of insulin resistance in obese girls during pubertal development. Horm Res Paediatr. 2013;80(5):363-70.
30. Finucane FM, Luan J, Wareham NJ, Sharp SJ, O'Rahilly S, Balkau B, et al. Correlation of the leptin:adiponectin ratio with measures of insulin resistance in non-diabetic individuals. Diabetologia. 2009 Nov;52(11):2345–9.

31. Chou H-H, Hsu L-A, Wu S, Teng M-S, Sun Y-C, Ko Y-L. Leptin-to-Adiponectin Ratio is Related to Low Grade Inflammation and Insulin Resistance Independent of Obesity in Non-Diabetic Taiwanese: A Cross-Sectional Cohort Study. Acta Cardiol Sin. 2014 May;30(3):204–14.

32. Adamska-Patruno E, Ostrowska L, Goscik J, Pietraszewska B, Kretowski A, Gorska M. The relationship between the leptin/ghrelin ratio and meals with various macronutrient contents in men with different nutritional status: a randomized crossover study. Nutr J. 2018 Dec 28;17(1):118.

33. Yang R, Barouch LA. Leptin signaling and obesity: cardiovascular consequences. Circ Res. 2007 Sep 14;101(6):545–59.

34. Kelesidis T, Kelesidis I, Chou S, Mantzoros CS. Narrative review: the role of leptin in human physiology: emerging clinical applications. Ann Intern Med. 2010 Jan 19;152(2):93–100.

35. Poetsch MS, Strano A, Guan K. Role of Leptin in Cardiovascular Diseases. Front Endocrinol (Lausanne). 2020;11:354.

36. Straub LG, Scherer PE. Metabolic Messengers: Adiponectin. Nat Metab. 2019 Mar;1(3):334–9.

37. Chandran M, Phillips SA, Ciaraldi T, Henry RR. Adiponectin: more than just another fat cell hormone? Diabetes Care. 2003 Aug;26(8):2442–50.

38. Ryan AS, Berman DM, Nicklas BJ, Sinha M, Gingerich RL, Meneilly GS, et al. Plasma adiponectin and leptin levels, body composition, and glucose utilization in adult women with wide ranges of age and obesity. Diabetes Care. 2003 Aug;26(8):2383–8.

39. Park K-G, Park K-S, Kim M-J, Kim H-S, Suh Y-S, Ahn J-D, et al. Relationship between serum adiponectin and leptin concentrations and body fat distribution. Diabetes Res Clin Pract. 2004 Feb;63(2):135–42.

40. Ohira T, Iso H. Cardiovascular disease epidemiology in Asia: an overview. Circ J. 2013;77(7):1646–52.

41. Ueshima H, Sekikawa A, Miura K, Turin TC, Takashima N, Kita Y, et al. Cardiovascular disease and risk factors in Asia: a selected review. Circulation. 2008 Dec 16;118(25):2702–9.

42. Nanditha A, Ma RCW, Ramachandran A, Snehalatha C, Chan JCN, Chia KS, et al. Diabetes in Asia and the Pacific: Implications for the Global Epidemic. Diabetes Care. 2016 Mar 1;39(3):472.

43. Ramachandran A, Snehalatha C, Shetty AS, Nanditha A. Trends in prevalence of diabetes in Asian countries. World J Diabetes. 2012 Jun 15;3(6):110–7.

44. Diefenbach MA, Leventhal H. The common-sense model of illness representation: Theoretical and practical considerations. Journal of Social Distress and the Homeless. 1996 Jan 1;5(1):11–38.

45. Hagger MS, Orbell S. A meta-analytic review of the common-sense model of illness representations. Psychology & Health. 2003;18(2):141–84.

46. Leventhal H, Phillips LA, Burns E. The Common-Sense Model of Self-Regulation (CSM): a dynamic framework for understanding illness self-management. J Behav Med. 2016 Dec;39(6):935–46.

47. Hagger MS, Orbell S. The common sense model of illness self-regulation: a conceptual review and proposed extended model. Health Psychol Rev. 2021 Feb 1;1–31.

48. Broadbent E, Petrie KJ, Main J, Weinman J. The brief illness perception questionnaire. J Psychosom Res. 2006 Jun;60(6):631–7.

49. Broadbent E, Wilkes C, Koschwanez H, Weinman J, Norton S, Petrie KJ. A systematic review and meta-analysis of the Brief Illness Perception Questionnaire. Psychol Health. 2015;30(11):1361–85.

50. Dobson R, Burgess MI, Sprung VS, Irwin A, Hamer M, Jones J, et al. Metabolically healthy and unhealthy obesity: differential effects on myocardial function according to metabolic syndrome, rather than obesity. Int J Obes (Lond). 2016 Jan;40(1):153–61.

51. Iacobini C, Pugliese G, Blasetti Fantauzzi C, Federici M, Menini S. Metabolically healthy versus metabolically unhealthy obesity. Metabolism. 2019 Mar;92:51–60.

52. Hinnouho G-M, Czernichow S, Dugravot A, Batty GD, Kivimaki M, Singh-Manoux A. Metabolically healthy obesity and risk of mortality: does the definition of metabolic health matter? Diabetes Care. 2013/05/01 ed. 2013 Aug;36(8):2294–300.

53. Smith GI, Mittendorfer B, Klein S. Metabolically healthy obesity: facts and fantasies. J Clin Invest. 2019 Oct 1;129(10):3978–89.

54. GERMAS - Gerakan Masyarakat Hidup Sehat [Internet]. Direktorat Promosi Kesehatan Kementerian Kesehatan RI. [cited 2021 Oct 18]. Available from: https://promkes.kemkes.go.id/germas

55. Li Y, Schoufour J, Wang DD, Dhana K, Pan A, Liu X, et al. Healthy lifestyle and life expectancy free of cancer, cardiovascular disease, and type 2 diabetes: prospective cohort study. BMJ. 2020 Jan 8;368:l6669.

56. Pate RR, Pratt M, Blair SN, Haskell WL, Macera CA, Bouchard C, et al. Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. JAMA. 1995 Feb 1;273(5):402–7.

57. Sofi F, Cesari F, Abbate R, Gensini GF, Casini A. Adherence to Mediterranean diet and health status: meta-analysis. BMJ. 2008 Sep 11;337:a1344.

58. Ruitenberg A, van Swieten JC, Witteman JCM, Mehta KM, van Duijn CM, Hofman A, et al. Alcohol consumption and risk of dementia: the Rotterdam Study. Lancet. 2002 Jan 26;359(9303):281–6.

59. Inoue-Choi M, Liao LM, Reyes-Guzman C, Hartge P, Caporaso N, Freedman ND. Association of Long-term, Low-Intensity Smoking With All-Cause and Cause-Specific Mortality in the National Institutes of Health-AARP Diet and Health Study. JAMA Intern Med. 2017 Jan 1;177(1):87–95.

60. Will JC, Galuska DA, Ford ES, Mokdad A, Calle EE. Cigarette smoking and diabetes mellitus: evidence of a positive association from a large prospective cohort study. International Journal of Epidemiology. 2001 Jun 1;30(3):540–6.

61. Warburton DER, Bredin SSD. Health benefits of physical activity: a systematic review of current systematic reviews. Curr Opin Cardiol. 2017 Sep;32(5):541–56.

62. Garralda-Del-Villar M, Carlos-Chillerón S, Diaz-Gutierrez J, Ruiz-Canela M, Gea A, Martínez-González MA, et al. Healthy Lifestyle and Incidence of Metabolic Syndrome in the SUN Cohort. Nutrients. 2018 Dec 30;11(1):65.

63. VanWormer JJ, Boucher JL, Sidebottom AC, Sillah A, Knickelbine T. Lifestyle changes and prevention of metabolic syndrome in the Heart of New Ulm Project. Preventive Medicine Reports. 2017 Jun 1;6:242–5.

64. Bhanushali CJ, Kumar K, Wutoh AK, Karavatas S, Habib MJ, Daniel M, et al. Association between Lifestyle Factors and Metabolic Syndrome among African Americans in the United States. J Nutr Metab. 2013;2013:516475.

65. de Mutsert R, den Heijer M, Rabelink TJ, Smit JWA, Romijn JA, Jukema JW, et al. The Netherlands Epidemiology of Obesity (NEO) study: study design and data collection. Eur J Epidemiol. 2013 Jun;28(6):513–23.

66. Kementerian Kesehatan Republik Indonesia, Badan Penelitian dan Pengembangan Kesehatan. RISKESDAS Tahun 2013 [Internet]. [cited 2021 Oct 18]. Available from: http://labdata.litbang.kemkes.go.id/riset-badan-litbangkes/menu-riskesnas/menu-riskesdas/374-rkd-2013

67. Kementerian Kesehatan Republik Indonesia, Badan Penelitian dan Pengembangan Kesehatan. RISKESDAS Tahun 2018 [Internet]. [cited 2021 Oct 18]. Available from: http://labdata.litbang.kemkes.go.id/riset-badan-litbangkes/menu-riskesnas/menu-riskesdas/426-rkd-2018

68. Park HS, Oh SW, Cho S-I, Choi WH, Kim YS. The metabolic syndrome and associated lifestyle factors among South Korean adults. International Journal of Epidemiology. 2004 Apr 1;33(2):328–36.

69. Wang Y, Tu R, Yuan H, Shen L, Hou J, Liu X, et al. Associations of unhealthy lifestyles with metabolic syndrome in Chinese rural aged females. Sci Rep. 2020 Feb 17;10(1):2718.

70. Gouveia ÉR, Gouveia BR, Marques A, Peralta M, França C, Lima A, et al. Predictors of Metabolic Syndrome in Adults and Older Adults from Amazonas, Brazil. Int J Environ Res Public Health. 2021 Feb 1;18(3):1303.

71. Yi Y, An J. Sex Differences in Risk Factors for Metabolic Syndrome in the Korean Population. Int J Environ Res Public Health. 2020 Dec 18;17(24):9513.

72. Aekplakorn W, Kessomboon P, Sangthong R, Chariyalertsak S, Putwatana P, Inthawong R, et al. Urban and rural variation in clustering of metabolic syndrome components in the Thai population: results from the fourth National Health Examination Survey 2009. BMC Public Health. 2011 Nov 10;11:854.

73. Dallongeville J, Cottel D, Ferrières J, Arveiler D, Bingham A, Ruidavets JB, et al. Household income is associated with the risk of metabolic syndrome in a sex-specific manner. Diabetes Care. 2005 Feb;28(2):409-15.

74. Song Q-B, Zhao Y, Liu Y-Q, Zhang J, Xin S-J, Dong G-H. Sex difference in the prevalence of metabolic syndrome and cardiovascular-related risk factors in urban adults from 33 communities of China: The CHPSNE study. Diab Vasc Dis Res. 2015 May;12(3):189–98.

75. Weng X, Liu Y, Ma J, Wang W, Yang G, Caballero B. An urban-rural comparison of the prevalence of the metabolic syndrome in Eastern China. Public Health Nutr. 2007 Feb;10(2):131–6.

76. Abdul-Rahim HF, Husseini A, Bjertness E, Giacaman R, Gordon NH, Jervell J. The metabolic syndrome in the West Bank population: an urban-rural comparison. Diabetes Care. 2001 Feb;24(2):275–9.

77. Arambepola C, Allender S, Ekanayake R, Fernando D. Urban living and obesity: is it independent of its population and lifestyle characteristics? Trop Med Int Health. 2008 Apr;13(4):448–57.

78. Han B, Chen Y, Cheng J, Li Q, Zhu C, Chen Y, et al. Comparison of the Prevalence of Metabolic Disease Between Two Types of Urbanization in China. Front Endocrinol (Lausanne). 2018 Nov 12;9:665–665.

79. Lindroth M, Lundqvist R, Lilja M, Eliasson M. Cardiovascular risk factors differ between rural and urban Sweden: the 2009 Northern Sweden MONICA cohort. BMC Public Health. 2014 Aug 9;14:825.

80. Tahapary DL, de Ruiter K, Martin I, van Lieshout L, Guigas B, Soewondo P, et al. Helminth infections and type 2 diabetes: a cluster-randomized placebo controlled SUGARSPIN trial in Nangapanda, Flores, Indonesia. BMC Infectious Diseases. 2015 Mar 18;15(1):133.

81. Kementerian Kesehatan Republik Indonesia, Badan Penelitian dan Pengembangan Kesehatan. Status Permintaan Data [Internet]. [cited 2021 Oct 18]. Available from: http://labdata.litbang.kemkes.go.id/menu-layan/status-permintaan-data