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The associations of leptin and adiponectin with the metabolic syndrome in an Indonesian and a Dutch population

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Asian;
Western

Abstract *Background and aims:* At the same BMI, Asian populations develop cardiometabolic complications earlier than Western populations. We hypothesized that a different secretion of the adipocyte-derived hormones leptin and adiponectin plays a role and investigated the associations of the two hormones with the metabolic syndrome (MetS) in an Indonesian and a Dutch population.

Methods and results: We performed cross-sectional analyses of the Netherlands Epidemiology of Obesity Study (n = 6602) and the SUGAR Scientific Programme Indonesia–Netherlands Study (n = 1461). We examined sex-stratified associations of leptin and adiponectin with MetS, using multivariate logistic regression including adjustment for total body fat. The mean (SD) leptin (mcg/L) were 4.7 (6.0) in Indonesian men, 18.6 (12.0) in Indonesian women, 9.1 (7.7) in Dutch men, and 23.4 (17.4) in Dutch women. The mean (SD) adiponectin (mg/L) were 5.7 (5.4), 7.5 (7.1), 6.6 (3.3), and 11.3 (4.9), respectively. Within the same BMI category, leptin concentrations were similar in the two populations, whereas adiponectin was lower in the Indonesian population. Per SD of leptin, adjusted prevalence odds ratios (ORs, 95%CI) of MetS were 0.9 (0.6–1.2) in Indonesian men, 1.1 (0.9–1.4) in Indonesian women, 2.2 (1.6–2.8) in Dutch men, and 1.2 (1.0–1.5) in Dutch women. Per SD of adiponectin, the ORs were 0.9 (0.7–1.2), 0.8 (0.7–1.0), 0.6 (0.6–0.8), and 0.4 (0.4–0.5), respectively.

Conclusions: Despite lower adiponectin levels, adiponectin was not related to the MetS in the Indonesian population and can not explain their increased cardiometabolic risk at the same BMI.

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Introduction

Asian populations develop cardiometabolic complications at a lower BMI than Western populations [1]. In fact, cut-offs for overall and abdominal obesity are lower in Asian populations, as their risks of diabetes mellitus and cardiovascular disease increase at an earlier stage than in Western populations (AHA/NHLBI, IDF, WHO) [2]. The difference in cardiometabolic risks between populations may partly be due to a different body fat distribution [3,4]. On average, Asians have a smaller subcutaneous adipose tissue compartment, and it is hypothesized that as obesity develops, their storage capacity is exhausted earlier than in Caucasians, and lipids may overflow earlier to the visceral compartment [4]. It is well-established that excess visceral adipose tissue is strongly associated with cardio-metabolic complications [5–12], which may in part explain the different cardiometabolic risks between ethnic populations at the same BMI.

The adipose tissue releases leptin and adiponectin, the two main adipocyte-derived hormones that play crucial roles in glucose homeostasis, insulin sensitivity, lipid metabolism, and platelet function [13–21]. In obesity, the enlarged adipocytes secrete more leptin but less adiponectin [13,15,22,23]. Increased leptin concentration, which is often accompanied by leptin resistance in obesity, induces oxidative stress in endothelial cells, stimulates the secretion of proinflammatory cytokines, and switches glucose metabolism to fatty acid oxidation [24–29]. In contrast, whereas adiponectin has insulin-sensitizing and anti-inflammatory properties, decreased adiponectin concentrations in obesity may lessen these protective effects mediated by the hormone [30–32].

Several studies conducted previously in Asian and Caucasian populations have revealed that (South) Asians have higher leptin but lower adiponectin concentrations than Caucasians [33–36]. We hypothesized that these different secretions of the adipocyte-derived hormones leptin and adiponectin play a role in the different cardiometabolic risks of the two populations. Therefore, in the present study, we aimed to investigate the levels and associations of leptin and adiponectin with the metabolic syndrome and its separate components in men and women in an Asian-Indonesian and a Caucasian-Dutch population. As it is still poorly understood to what extent the difference in leptin and adiponectin may mediate the difference in cardiometabolic risks between the two populations, findings from this study may potentially contribute to explain the increased cardiometabolic risk of the Asian population at the same BMI.

Methods

Study designs and populations

This study consists of cross-sectional analyses of baseline measurements of the Netherlands Epidemiology of Obesity (NEO) Study and the SUGAR Scientific Program Indonesia–Netherlands (SUGARSPIN) Study.

The Netherlands epidemiology of obesity study

The NEO study is a population-based prospective cohort study designed to investigate pathways that lead to obesity-related disease. Between 2008 and 2012, the NEO study included 6671 men and women aged 45–65 years, with an oversampling of individuals with overweight or obesity. The NEO study is conducted in Leiden and its surroundings, the Netherlands, with the majority (95%) of the population White-Caucasian. The Medical Ethical Committee of the Leiden University Medical Center (LUMC) had approved the NEO study design, and all participants gave informed consent. Detailed information about the NEO study design and data collection had been described previously [37].

The Indonesian SUGARSPIN study

The SUGARSPIN study is a randomized controlled trial aimed to examine the effect of parasitic infection on insulin resistance and cardio-metabolic health. The SUGARSPIN Study is conducted in the subdistrict of Nangapanda, Ende, Flores, Indonesia. The population was adult $\geq$16 years old, nonpregnant, that was randomized at the household level. All participants in the SUGARSPIN study are Malay-Austronesian. The study was approved by the ethics committee of Faculty of Medicine, Universitas Indonesia (FKUI) (ref: 549/H2·F1/ETIK/2013), and filed by the ethics committee of Leiden University Medical Center (LUMC). All participants gave their written informed consent. A detailed study protocol of the SUGARSPIN trial had been published previously [38]. For the present study, we used baseline data of the SUGARSPIN trial before any interventions were commenced. Participants younger than 18 years of age were excluded.

Data collection

The present study includes all participants from both studies with complete measurements on serum leptin and adiponectin concentrations, anthropometry (BMI, waist circumference, and total body fat), blood pressure, fasting plasma glucose, and serum cholesterol and triglyceride concentrations. Participants were instructed to fast overnight before blood sampling at the study center.

Participants from both studies completed questionnaires with information on demographic characteristics and risk factors such as age, sex, highest completed level of education, smoking behavior, alcohol consumption, pre-existing cardiovascular disease, stroke, diabetes, and familial history of these diseases. Data on physical activity during leisure time was available in the Dutch population as collected via SQUASH questionnaire, in which participants reported the frequency and duration of their physical activity in leisure time, which was expressed in hours per week of metabolic equivalents (MET-h/week) [37]. Information on physical activity was not available in the Indonesian population.

Assessment of leptin and adiponectin concentrations

In the NEO Study, serum leptin was measured with a human leptin competitive RadioImmunoAssay (RIA) (Cat Nr HL-81HK, Merck Millipore, Darmstadt, Germany). A gamma counter Wizard 2 3470, PerkinElmer, StatLia software, was used to determine the concentration. Coefficients of leptin variation were calculated based on 22 runs over 105 days and were 12–14% at concentrations between 19 and 55 μg/L. Serum total adiponectin was measured on an automated analyzer (Roche Modular P800) using a latex particle-enhanced turbidimetric immunoassay (Cat Nr A0299, Randox Laboratories Limited) [39].

In the SUGARSPIN Study, serum leptin and total adiponectin were measured by ELISA using commercial reagents (DuoSet ELISA R&D System Europe Ltd, Abingdon, UK) according to the manufacturer's protocol. The inter- and intra-assay coefficients of variance (CV) of leptin were 2.2% and 3.2%. While for adiponectin, the inter- and intra-assay CV were 3.1% and 7.0%, respectively [40].

Assessment of the metabolic syndrome

The Metabolic Syndrome was defined by the Joint Interim Statement criteria as the co-occurrence of at least three out of the following five cardio-metabolic abnormalities: abdominal obesity, hypertension, hyperglycemia, hypertriglyceridemia, and low HDL-cholesterol. The detailed criteria and ethnic-specific cut-offs were described in [Supplemental Table 1] [2].

In both populations, waist circumference was measured halfway between the iliac crest and the lowest rib using a flexible steel tape measure to the nearest 0.1 cm (SECA Model 201, Seca Gmbh Co, Hamburg, Germany). Blood pressure was obtained by a digital sphygmomanometer at the left arm, at the upright sitting position, after 5 min rest (HEM-7200, Omron Healthcare Co, Ltd, Kyoto, Japan). The average of three measurements was used for analysis.

In the NEO Study, fasting plasma glucose was determined using a standard clinical chemistry method (Roche Modular P800 Analyzer, Roche Diagnostics, Mannheim, Germany). In the SUGARSPIN Study, glucose concentrations were measured with fingertip capillary blood test (Breeze®2 glucose meter, Bayer Health Care LLC, Basel, Switzerland). In both the NEO and SUGARSPIN studies, analyses of cholesterol and triglyceride concentrations were performed at the LUMC and determined based on enzymatic colorimetric methods (Roche Modular P800 Analyzer, Roche Diagnostics, Mannheim, Germany).

Measures of body fat

In the Dutch population, body weight (kg) and total body fat (%) were estimated with bipolar bioelectrical impedance analysis (BIA) (TBF-310, Tanita International Division, UK). In the Indonesian population, body weight was measured with a flat scale for mobile use (SECA Model 876, Seca Gmbh Co, Hamburg, Germany), while total body fat was estimated with bipolar BIA (TBF-300A, Tanita Corp, Tokyo, Japan) [41]. Body mass index (BMI) was calculated by dividing body weight (kg) by the square of height (m^2).

Statistical analysis

Statistical analyses were performed using STATA Statistical Software (StataCorp, College Station, TX, USA), version 14. To correct for the oversampling of individuals with BMI $\geq$27 kg/m2 in the NEO study, analyses in the NEO study were weighted towards the BMI distribution of the general Dutch population. As a result, the results apply to a population-based study without oversampling of individuals with a BMI $\geq$27 kg/m^2.

Characteristics were presented as percentage (%) for categorical variables, and mean (SD) or median (25th, 75th percentiles) for continuous variables, stratified by sex (men or women) and ethnicity (Indonesian or Dutch). Because the BMI distribution may be different in the Indonesian and the Dutch population, we also calculated all characteristics stratified by BMI category according to the WHO classifications for Asian and Caucasian populations [Supplemental Table 2]. In this present study, we combined the two classifications by using the Caucasian classification with an additional BMI category of 23.0–24.9 kg/m^2 to comply with WHO classification for Asian populations.

We calculated sex- and population-specific Z-scores and standardized the values of leptin and adiponectin to a mean of zero and an SD of one. Logistic regression analyses were performed to calculate the prevalence odds ratios [ORs (95% CI)] of the metabolic syndrome and its components, associated per SD of leptin and adiponectin. Linear regression analyses were performed to examine the strength of associations of leptin and adiponectin with the components of the metabolic syndrome (per cm for waist circumference, per mmHg for blood pressure, per mmol/L for fasting glucose, triglyceride, and HDL-cholesterol).

To control for potential confounding factors, multivariable analyses were adjusted for age, education, smoking status, alcohol consumption, pre-existing diseases (CVD, stroke, diabetes), and familial history of the diseases. Additionally, because total body fat is a common cause of leptin, adiponectin, and the metabolic syndrome, and therefore plays a role as a confounding factor [23,29,42–44], we further adjusted the associations for total body fat. We presented both odds ratios before and after adjusting for total body fat to show the influence of adjustment for total body fat. A diagram illustrating the hypothesized relation between leptin, adiponectin, and metabolic syndrome, including confounding factors is available in Supplemental Fig. 1.

To investigate whether the associations may differ between different BMI categories, we repeated the regression analyses after stratifying by BMI. We tested for interaction with BMI by including product terms of leptin and adiponectin with the BMI-obese category in the regression models of the metabolic syndrome. We used the BMI cut-offs of $\geq$25.0 for the Indonesian and $\geq$30.0 for the Dutch population. We defined statistically significant interaction as a p-value of $<$0.05.

Table 1 Characteristics of the Indonesian and the Dutch populations.

a. Characteristics of the Indonesian Population

	Men (n = 564; 39%)						Women (n = 897; 61%)					
	Total	BMI <18.5	BMI 18.5 −22.9	BMI 23.0 −24.9	BMI 25.0 −29.9	BMI >30.0	Total	BMI <18.5	BMI 18.5 −22.9	BMI 23.0 −24.9	BMI 25.0 −29.9	BMI >30.0
%	**100**	14	50	14	20	2	**100**	13	42	15	24	6
Age (y)	**45.8**	44.1	47.0	45.1	45.2	39.8	**42.8**	45.3	41.4	44.2	43.1	41.8
	(14.2)	(19.5)	(14.1)	(13.2)	(10.7)	(11.4)	**(14.4)**	(18.8)	(15.4)	(12.2)	(11.6)	(10.9)
Education (% High)	**14**	1	5	3	4	1	**11**	1	5	2	2	1
Current Smokers (%)	**45**	6	22	5	11	1	**0**	0	0	0	0	0
Alcohol Consumption*	**25**	2	13	4	6	0	**2**	0	1	0	1	0
Family History of T2D (%)	**8**	1	4	1	1	1	**9**	1	3	1	3	1
Pre-existing Diabetes (%)	**7**	0	3	2	2	0	**6**	0	2	1	2	1
Leptin (mcg/L)	**4.7**	1.1	2.5	6.1	9.8	17.2	**18.6**	6.0	13.7	22.0	28.1	32.3
	(6.0)	(0.9)	(3.4)	(5.6)	(7.3)	(8.7)	**(12.0)**	(4.5)	(8.8)	(9.8)	(10.3)	(9.1)
Adiponectin (mg/L)	**5.7**	7.0	6.0	4.9	4.8	3.4	**7.5**	9.9	7.9	7.0	6.2	5.6
	(5.4)	(6.0)	(4.8)	(5.4)	(6.3)	(2.9)	**(7.1)**	(9.1)	(7.5)	(5.4)	(6.1)	(4.6)
Leptin/Adiponectin Ratio	**1.6**	0.2	0.7	2.2	3.2	10.1	**4.7**	1.1	3.0	5.9	7.4	10.1
	(2.9)	(0.3)	(1.4)	(2.5)	(2.9)	(9.6)	**(5.5)**	(1.3)	(3.0)	(6.8)	(5.7)	(8.8)
Total Body Fat (%)	**21.7**	13.6	19.2	25.2	29.1	35.7	**33.3**	20.0	29.0	36.0	42.1	49.7
	(6.7)	(3.1)	(3.9)	(3.2)	(4.7)	(3.8)	**(9.2)**	(3.9)	(4.1)	(3.8)	(4.6)	(6.2)
Body Mass Index (kg/m^2)	**22.2**	17.4	20.7	24.1	26.8	32.0	**23.0**	17.0	20.9	24.0	27.0	32.0
	(3.6)	(0.9)	(1.3)	(0.6)	(1.3)	(1.7)	**(4.2)**	(1.3)	(1.3)	(0.6)	(1.4)	(2.0)
Waist Circumference (cm)	**78.0**	64.4	73.2	84.3	91.7	102.2	**77.6**	61.5	71.7	81.1	88.9	99.0
	(11.2)	(3.5)	(6.0)	(5.4)	(5.8)	(7.1)	**(12.4)**	(5.2)	(6.7)	(6.8)	(7.4)	(7.1)
Fasting Glucose (mmol/L)	**5.5**	5.0	5.4	5.7	5.7	5.2	**5.5**	5.2	5.4	5.5	5.7	5.9
	(1.4)	(0.4)	(1.4)	(1.8)	(1.5)	(0.5)	**(1.5)**	(0.6)	(1.8)	(1.1)	(1.4)	(1.8)
Systolic BP (mmHg)	**132.7**	128.7	132.2	134.2	135.3	136.8	**129.3**	125.5	126.1	131.3	135.0	132.8
	(22.6)	(24.8)	(23.2)	(22.1)	(20.1)	(19.3)	**(24.4)**	(22.3)	(24.3)	(21.9)	(26.9)	(21.1)
Diastolic BP (mmHg)	**77.2**	74.3	75.8	77.9	81.8	82.0	**77.0**	73.6	74.8	77.8	81.5	80.0
	(12.1)	(12.4)	(12.2)	(10.4)	(11.5)	(10.7)	**(12.0)**	(10.6)	(11.4)	(10.7)	(13.5)	(9.7)
Triglycerides (mmol/L)	**1.6**	1.2	1.4	1.8	2.0	2.4	**1.4**	1.2	1.3	1.4	1.6	1.7
	(0.7)	(0.4)	(0.5)	(0.7)	(0.9)	(0.9)	**(0.7)**	(0.4)	(0.6)	(0.6)	(0.9)	(0.5)
HDL-Cholesterol (mmol/L)	**1.1**	1.2	1.1	1.0	1.0	1.0	**1.3**	1.4	1.4	1.2	1.2	1.1
	(0.3)	(0.3)	(0.3)	(0.2)	(0.3)	(0.3)	**(0.3)**	(0.4)	(0.4)	(0.3)	(0.3)	(0.3)
Metabolic Syndrome (%)	**26**	0	6	5	13	2	**33**	1	6	7	15	4
Abdominal Obesity (%)	**17**	0	0	3	12	2	**41**	0	5	8	22	6
Hyperglycemia (%)	**28**	1	15	5	7	0	**31**	3	10	6	10	3
Hypertension (%)	**47**	5	22	7	12	1	**39**	4	13	8	11	3
Hypertriglyceridemia (%)	**33**	1	12	7	11	2	**24**	2	7	4	8	3
Low HDL-Cholesterol (%)	**42**	3	17	8	12	2	**55**	5	19	10	16	5

b. Characteristics of the Dutch Population

	Men (n = 3103; 44%)						Women (n = 3433; 56%)					
	Total	BMI <18.5	BMI 18.5 −22.9	BMI 23.0 −24.9	BMI 25.0 −29.9	BMI >30.0	Total	BMI <18.5	BMI 18.5 −22.9	BMI 23.0 −24.9	BMI 25.0 −29.9	BMI >30.0
%	**100**	0	11	22	51	16	**100**	1	30	19	34	16
Age (y)	**56.0**		57.0	55.9	55.8	56.0	**55.4**	56.1	55.0	55.4	55.6	55.5
	(6.3)		(3.2)	(3.1)	(6.3)	(10.2)	**(5.8)**	(2.7)	(3.2)	(3.2)	(5.8)	(10.0)
Education (% High)	**48**		6	12	25	5	**44**	0	17	10	13	4
Current Smokers (%)	**18**		2	3	10	3	**14**	0	5	2	5	2
Alcohol Consumption*	**16.2**		12.5	5.7	16.6	15.6	**7.6**	2.8	8.2	7.2	8.0	3.2
	(5.7		(6.5	(16.7	(5.8	(4.3	**(1.5**	(1.8	(3.1	(1.4	(1.6	(0.2
	−28.1)		−24.0)	−30.4)	−27.7)	−30.7)	**−14.8)**	−4.4)	−15.6)	−14.5)	−15.6)	−12.0)
Family History of T2D (%)	**27**		3	5	14	5	**33**	0	8	7	11	7
Pre-existing Diabetes (%)	**7**		0	1	3	3	**4**	0	0	1	1	2
Leptin (mcg/L)	**9.1**		3.7	5.7	8.9	18.2	**23.4**	5.4	11.1	17.6	26.4	47.8
	(7.7)		(1.2)	(1.9)	(5.8)	(17.3)	**(17.4)**	(1.9)	(3.1)	(3.9)	(12.1)	(41.6)
Adiponectin (mg/L)	**6.6**		8.5	7.1	6.2	5.8	**11.3**	15.7	12.5	11.9	10.8	9.3
	(3.3)		(1.9)	(1.8)	(2.9)	(4.6)	**(4.9)**	(3.3)	(2.8)	(2.7)	(4.8)	(7.2)
Leptin/Adiponectin Ratio	**1.8**		0.5	1.1	1.8	4.1	**2.8**	0.4	1.1	1.8	3.0	6.6
	(2.4)		(0.2)	(0.5)	(1.6)	(7.3)	**(3.1)**	(0.1)	(0.4)	(0.6)	(2.3)	(9.0)

(*continued on next page*)

Table 1 (*continued*)

b. Characteristics of the Dutch Population

	Men (n = 3103; 44%)						Women (n = 3433; 56%)					
	Total	BMI <18.5	BMI 18.5 −22.9	BMI 23.0 −24.9	BMI 25.0 −29.9	BMI >30.0	Total	BMI <18.5	BMI 18.5 −22.9	BMI 23.0 −24.9	BMI 25.0 −29.9	BMI >30.0
Total Body Fat (%)	**25.0**		17.4	20.8	25.8	33.8	**36.8**	20.0	30.5	35.1	39.4	46.1
	(6.1)		(1.4)	(1.3)	(3.3)	(9.0)	**(6.4)**	(2.5)	(2.2)	(1.8)	(3.3)	(6.0)
Body Mass Index (kg/m^2)	**26.9**		21.8	24.1	27.2	33.3	**25.9**	18.0	21.4	24.0	27.0	34.5
	(3.9)		(0.5)	(0.3)	(1.4)	(5.4)	**(4.7)**	(0.2)	(0.6)	(0.3)	(1.4)	(7.2)
Waist Circumference(cm)	**98.4**		84.9	90.7	99.5	115.0	**87.2**	68.3	75.8	82.3	91.2	107.0
	(11.4)		(2.6)	(2.6)	(6.5)	(15.4)	**(12.6)**	(1.3)	(3.1)	(3.1)	(7.4)	(18.0)
Fasting Glucose (mmol/L)	**5.7**		5.3	5.5	5.7	6.2	**5.3**	5.1	5.0	5.2	5.4	5.8
	(1.2)		(0.3)	(0.6)	(1.0)	(2.5)	**(0.8)**	(0.1)	(0.3)	(0.4)	(0.7)	(1.9)
Systolic BP (mmHg)	**134.4**		129.6	133.0	134.6	139.2	**126.8**	122.7	124.0	127.0	127.7	130.3
	(16.1)		(7.7)	(7.6)	(16.1)	(25.9)	**(16.9)**	(8.7)	(9.4)	(8.9)	(17.0)	(29.0)
Diastolic BP (mmHg)	**84.8**		81.3	83.4	85.2	87.9	**81.9**	80.0	79.0	81.5	83.1	85.1
	(10.5)		(5.5)	(4.8)	(10.4)	(16.7)	**(9.9)**	(4.4)	(5.3)	(5.1)	(10.1)	(17.2)
Triglycerides (mmol/L)	**1.4**		0.8	1.3	1.5	1.8	**1.1**	0.6	0.9	1.0	1.2	1.4
	(1.0)		(0.2)	(0.5)	(0.9)	(2.0)	**(0.7)**	(0.1)	(0.2)	(0.4)	(0.7)	(1.3)
HDL-Cholesterol(mmol/L)	**1.3**		1.6	1.4	1.3	1.2	**1.8**	2.3	2.0	1.8	1.6	1.5
	(0.4)		(0.2)	(0.2)	(0.3)	(0.4)	**(0.4)**	(0.2)	(0.2)	(0.2)	(0.4)	(0.6)
Metabolic Syndrome (%)	**36**		1	4	19	12	**24**	0	2	2	10	10
Abdominal Obesity (%)	**35**		0	0	19	16	**44**	0	1	4	23	16
Hyperglycemia (%)	**41**		2	7	22	10	**23**	0	3	3	9	8
Hypertension (%)	**70**		6	14	36	14	**55**	0	13	10	20	12
Hypertriglyceridemia (%)	**35**		1	5	20	9	**18**	0	2	3	7	6
Low HDL-Cholesterol (%)	**27**		1	4	15	7	**20**	0	2	3	8	7

Data were presented in means (SD) or %. Results in the NEO Study were based on analyses weighted towards a normal BMI distribution in the Dutch population. ˆindicating a not normal distribution; presented in median (25th-75th percentiles). *Alcohol Consumption was measured in **% current drinkers** (in the Indonesian) and **gram/day** intake (in the Dutch population).

As the Indonesian population consisted of adult individuals with a wide age range (16–86 years), we repeated the analyses after restricting to the subgroup of individuals aged 45–65 (n = 574). Also, to investigate whether physical activity may influence the exposure-outcome associations, we performed an additional analysis in the Dutch population, adjusting for physical activity during leisure time in the linear and logistic regression models.

Finally, because the leptin/adiponectin ratio has been suggested as an index to estimate adipose tissue dysfunction or even a biomarker of adipose tissue inflammation [45,46], we also performed regression analyses to examine the associations of the leptin/adiponectin ratio with the metabolic syndrome and its components.

Results

Characteristics of the Indonesian and the Dutch populations

After exclusion of participants <18 years old (n = 105) and participants with missing values of leptin, adiponectin, BMI, total body fat, and the components of the metabolic syndrome (n = 103), 1461 participants from the Indonesian population were included in the analyses. After excluding participants with missing variables (n = 69), 6602 participants from the Dutch populations were included in the present study.

Table 1a and b displays the characteristics of the Indonesian and the Dutch populations stratified by ethnicity, sex, and BMI. The Dutch population was generally older and more often highly educated than the Indonesian population. Dutch men and women reported nearly four times higher familial history of diabetes than Indonesian men and women.

The mean (SD) leptin concentrations (mcg/L) were 4.7 (6.0) in Indonesian men, 18.6 (12.0) in Indonesian women, 9.1 (7.7) in Dutch men, and 23.4 (17.4) in Dutch women. The mean (SD) adiponectin concentrations (mg/L) were 5.7 (5.4), 7.5 (7.1), 6.6 (3.3), and 11.3 (4.9), respectively. Although on average leptin concentrations were higher in the Dutch population, within the same BMI category leptin levels did not differ much between populations [Table 1a and b]. Adiponectin concentrations were consistently lower in the Indonesian than in the Dutch population, both in the total population and within the same BMI category [Table 1a and b].

In both populations, women had more total body fat than men. It was 21.7 (6.7) in Indonesian men, 33.3 (9.2) in Indonesian women, 25.0 (6.1) in Dutch men, and 36.8 (6.4) in Dutch women. The proportions of abdominal obesity according to ethnic-specific waist circumference cut-offs were 17% in Indonesian men, 41% in Indonesian

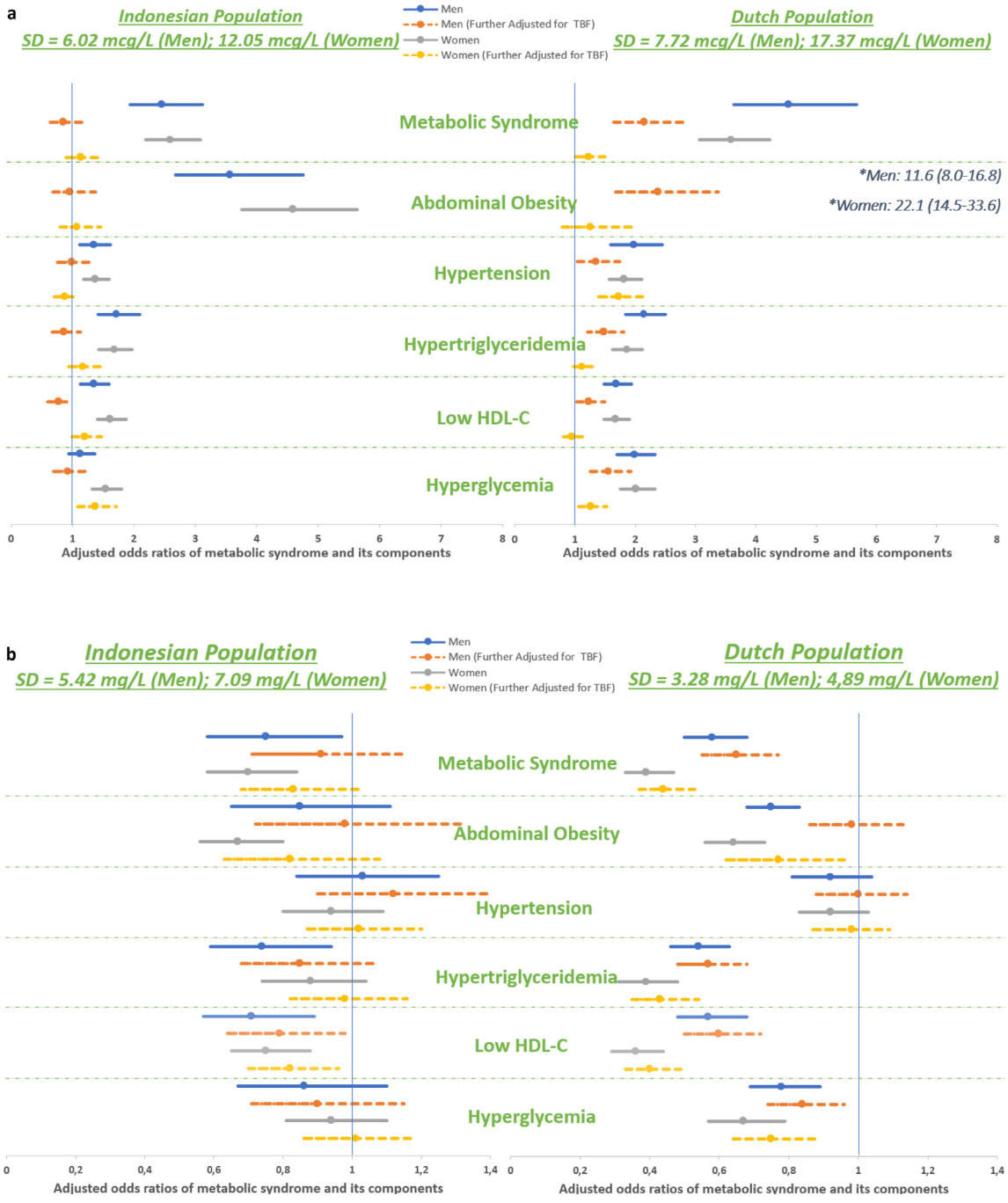

Figure 1 **a**. The associations of Leptin with the metabolic syndrome and its components. The forest plot showed the adjusted Odds Ratios of the Metabolic Syndrome and its components per 1 SD of Leptin in the Indonesian and the Dutch population. **b**. The associations of Adiponectin with the metabolic syndrome and its components. The forest plot showed the adjusted Odds Ratios of the Metabolic Syndrome and its components per 1 SD of Adiponectin in the Indonesian and the Dutch population. Data were presented in OR (95%CI). Associations were adjusted for age, education, alcohol consumption, smoking behavior, familial history of DM, and previous diagnosis of DM, and were further adjusted for total body fat.

women, 35% in Dutch men, and 44% in Dutch women. The prevalence of metabolic syndrome was 30% in the Indonesian population and 29% in the Dutch population.

The associations of leptin with the metabolic syndrome and its components

In both the Indonesian and the Dutch populations, leptin was positively associated with metabolic syndrome. Per SD of leptin, adjusted ORs (95% CIs) were 2.46 (1.94–3.12) in Indonesian men, 2.60 (2.19–3.09) in Indonesian women, 4.55 (3.64–5.68) in Dutch men, and 3.60 (3.07–4.23) in Dutch women. These associations attenuated after additional adjustment for total body fat [OR (95% CI): 0.86 (0.64–1.16) in Indonesian men, 1.14 in Indonesian women (0.90–1.45), 2.16 (1.65–2.82) in Dutch men, and 1.23 (1.01–1.50) in Dutch women] [Fig. 1a]. Likewise, after adjusting for total body fat, leptin was not associated with

the components of the metabolic syndrome in the Indonesian population. In the Dutch population, all five components of the metabolic syndrome contributed to the association with leptin [Fig. 1a, Supplemental Table 3a].

The associations of adiponectin with the metabolic syndrome and its components

In both the Indonesian and the Dutch populations, adiponectin was negatively associated with metabolic syndrome. Per SD of adiponectin, adjusted OR (95% CI) were 0.75 (0.58–0.97) in Indonesian men, 0.70 (0.58–0.84) in Indonesian women, 0.58 (0.50–0.68) in Dutch men, and 0.39 (0.33–0.47) in Dutch women. These associations attenuated after further adjustment for total body fat, to an OR (95% CI) of 0.91 (0.71–1.16) in Indonesian men, 0.83 (0.68–1.02) in Indonesian women, 0.65 (0.55–0.77) in Dutch men, and 0.44 (0.37–0.53) in Dutch women [Fig. 1b].

In the Indonesian population, adiponectin was only negatively associated with low HDL-cholesterol. In the Dutch population, in addition to low HDL, adiponectin was also associated with hypertriglyceridemia and hyperglycemia [Fig. 1b, Supplemental Table 3b].

Leptin/adiponectin ratio and the metabolic syndrome

The mean (SD) leptin/adiponectin ratio were 1.6 (2.9) in Indonesian men, 4.7 (5.5) in Indonesian women, 1.8 (2.4) in Dutch men, and 2.8 (3.1) in Dutch women. Whereas not associated in the Indonesian population, in the Dutch population the associations of metabolic syndrome with leptin/adiponectin ratio were relatively stronger than with leptin or adiponectin alone. In both populations, all associations attenuated after further adjustment for total body fat [Supplemental Fig. 2 and Supplemental Table 3c].

Sensitivity analyses

Although interaction terms between BMI with leptin, but not with adiponectin, were statistically significant in their association with the metabolic syndrome, we observed no large differences in the associations of leptin and adiponectin with the metabolic syndrome between BMI categories [Supplemental Fig. 3a and b].

After repeating the regression analyses in the subgroup of individuals aged 45–65 in the Indonesian population (n = 574; 41% men), the observed results were similar to the total Indonesian population [Supplemental Fig. 4]. After additional adjustment for physical activity in the regression analyses of the Dutch population, the results did not notably change [Supplemental Table 3a, 3b, and 3c].

Discussion

In the present study, we hypothesized that differences in the adipocyte-derived hormones leptin and adiponectin in part explain the early development of cardiometabolic complications in Asian populations compared with Western populations, and we investigated leptin and adiponectin concentrations in relation to the metabolic syndrome in men and women in an Asian-Indonesian and a Caucasian-Dutch population.

Whereas leptin concentrations were similar in both populations within the same BMI range, adiponectin concentrations were lower in the Indonesian population than in the Dutch population. Total body fat strongly influenced the associations of leptin and adiponectin with metabolic syndrome, particularly in the Indonesian population whose associations disappeared after adjustment for total body fat. Despite lower adiponectin levels, adiponectin was not related to the risk of metabolic syndrome in the Indonesian population, and therefore, cannot explain their increased cardiometabolic risk at the same BMI.

Previous studies observed that South Asians (Indian) had on average higher, whereas East Asians (Chinese) had lower, levels of leptin concentrations than Caucasians [33–36]. However, these studies did not provide details on the differences in leptin concentrations between populations within the same BMI range. Our study observed that, although on average leptin concentrations were lower in the Indonesian population, within the same BMI range leptin concentrations hardly differed from the Dutch population. This suggests that the leptin production per gram of adipose tissue, and therefore the metabolic activity of the adipose tissue with regard to leptin, is comparable between populations. Nevertheless, whereas leptin was positively associated with the metabolic syndrome in the Dutch population, the associations of leptin with the metabolic syndrome and its components were absent in the Indonesian population after adjustment for total body fat.

Our observation that total body fat strongly influenced the relationship between leptin and metabolic syndrome is aligned with previous studies, which reported strong associations between leptin and total body fat [23,39,42], partly due to the nature of leptin as an endogenous secretion product of adipose tissue [43,44]. In relation to the metabolic syndrome, our results in the Dutch population are supported by two Mendelian randomization studies on leptin. One Mendelian randomization study showed a causal relation between leptin and HOMA-IR, which may explain the association between leptin and type 2 diabetes [47], whereas another Mendelian randomization study showed that leptin was also potentially causally associated with blood pressure, particularly among current smokers [48]. The findings of these two studies, which were conducted in a White/European descent majority population, support our observations of positive associations between leptin with hyperglycemia and hypertension in the Dutch population. It remains unclear why we did not observe any relation between leptin and metabolic syndrome in the Indonesian population. Although differences in genetic make-up and measurement error may contribute to these findings [49,50], it may

be possible that the metabolic activity of adipose tissue plays a different role in relation to cardiometabolic health in Asian populations.

In contrast to leptin, previous studies have observed that Asian populations (including Indian, Chinese, and Japanese descent) had lower adiponectin levels than Caucasians [33–36], which were consistent with our findings. Adiponectin is known for its insulin-sensitizing and anti-inflammatory properties [30–32], and previous studies in the Asian population reported that total adiponectin was inversely associated with HOMA-IR [35,36]. In this study, we observed no association between adiponectin and the risk of metabolic syndrome and its components in the Indonesian population. Nevertheless, the absence of association in our study is consistent with a previous Mendelian randomization study on adiponectin, which showed that adiponectin is not causally related to T2D and glucose homeostasis [51]. This may mean that the association between adiponectin and metabolic syndrome that we observed in the Dutch population is mainly explained by confounding. Furthermore, the lower level of adiponectin in the Indonesian population may also be explained by the under-expression of this lipogenic marker by omental fat, particularly when type 2 diabetes was present [52]. Instead, the enhancement of low-grade systemic inflammation in omental adipose tissue, which leads to metabolic complications, is more associated with an overexpression of other markers, such as CD14 and IL-18 [52].

Whereas leptin/adiponectin ratio was also not associated with the metabolic syndrome in the Indonesian population after adjustment for total body fat, it remained positively associated in the Dutch population. In fact, the leptin/adiponectin ratio was more strongly associated with metabolic syndrome than leptin or adiponectin alone. This was consistent with previous studies which observed that the associations of leptin/adiponectin ratio with the metabolic syndrome and insulin resistance were greater than the association with leptin or adiponectin alone [13,19]. This may imply the better potential of leptin/adiponectin ratio as a biomarker of the metabolic syndrome, reflecting a pro/anti-inflammatory balance, rather than leptin or adiponectin alone.

Although it was well-established that Asians develop cardiometabolic complications earlier than the Western population at the same BMI [1–4], 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 within the same BMI category. Our finding shows that despite the lower levels of adiponectin in the Indonesian population, presumably due to more abdominal fat at the same BMI, adiponectin was not related to the risk of the metabolic syndrome in the Indonesian population and did not provide an explanation of their increased cardiometabolic risk at the same BMI.

A strength of the present study is the availability of leptin and adiponectin concentrations in large study populations of the two countries, with which we could investigate the ethnic variation of leptin and adiponectin and their associations with the metabolic syndrome. However, several limitations need to be considered. First, due to the cross-sectional and observational nature of the present study, residual confounding always remains possible. Second, there is a possible underestimation of hypertension, hypertriglyceridemia, and low HDL-cholesterol in the Indonesian population, as the use of antihypertensive and lipid-lowering agents were not recorded in the study. Third, different measurement methods for glucose, leptin, and adiponectin were used in the Indonesian and the Dutch population. Nevertheless, a previous study on the accuracy of the capillary glucometer that was used in the present study observed that more than 92% results were within Zone A of Parkes error grid analysis compared to laboratory plasma glucose test, indicating a clinically comparable measurement [53]. Also, previous studies comparing the comparability of leptin and adiponectin measurements by using ELISA and RIA observed a strong correlation between the two methods ($r > 0.95$ for leptin, $r > 0.92$ for adiponectin) [54,55], with a reported Bland-Altman mean difference (mg/L) for adiponectin of -0.34 ± 2.02. This implies that the observed differences in adiponectin between methods were sufficiently minor and will not influence the interpretation of our results [55]. Fourth, it must be noted that the SUGARSPIN study population represents an Indonesian population living in rural areas of Indonesia, hence results from this present study 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, which may support the generalizability of our results to the greater Indonesian population [40]. Fifth, We included different age groups for the two populations (aged >18 in the Indonesian population, aged 45–65 in the Dutch population). Nevertheless, when restricting our analyses to individuals aged 45–65 in the Indonesian population, results were similar. Sixth, the unavailability of data on physical activity in the Indonesian population hindered us from investigating how it may contribute to the different risks of metabolic syndrome between the two populations, associated with leptin and adiponectin. However, after additional adjustment for physical activity in the Dutch population, the exposure-outcome associations remained unaltered, suggesting that physical activity is not a major confounding factor in these associations. Finally, we could only consider metabolic syndrome as the outcome variable, and therefore, our results do not apply to the relations of leptin and adiponectin with other cardiometabolic endpoints, such as type 2 diabetes and cardiovascular disease.

In conclusion, within the same BMI range, the Indonesian population had lower adiponectin concentrations than the Dutch population. Nevertheless, both leptin and adiponectin were not related to the risk of metabolic syndrome in the Indonesian population, and therefore cannot explain their increased cardiometabolic risk at the same BMI. The influence of total and abdominal fat on cardiometabolic health risks in Asian populations via other

pathways than via leptin and adiponectin, as well as the direct influence of leptin and adiponectin with cardiovascular endpoints via other pathways than the metabolic syndrome, should be investigated in further studies.

Declaration of competing interest

The NEO study is supported by the participating Departments, the Division and the Board of Directors of the Leiden University Medical Centre, and by the Leiden University, Research Profile Area 'Vascular and Regenerative Medicine'. The first author receives a PhD scholarship from the Indonesia Endowment Fund for Education (LPDP). The authors declare that they have no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2021.05.012.

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