

Original Article

High prevalence of low HDL-c in the Philippines compared to the US: population differences in associations with diet and BMI

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Cardiovascular disease (CVD) is a leading cause of death in the Philippines, although few studies here have examined the lipid profiles underlying disease risk. The isolated low high density lipoprotein cholesterol (HDL-c) phenotype has been implicated as a CVD risk factor, the prevalence of which exhibits significant variation across populations. To assess population variation in individual lipid components and their associations with diet and anthropometric characteristics, we compare lipid profiles in a population of adult Filipino women (n=1877) to US women participating in the National Health and Nutrition Examination Survey (NHANES, n=477). We conducted multiple regression models to assess the relationship between lipid components, body mass index, and dietary variables in the two populations. We measured the prevalence of lipid phenotypes, and logistic regression models determined the predictors of the isolated low HDL-c phenotype. High density lipoprotein cholesterol was lower in the Philippines (40.8±0.2 mg/dL) than in NHANES (60.7±0.7 mg/dL). The prevalence of the isolated low HDL-c phenotype was 28.8%, compared to 2.10% in NHANES. High prevalence among Filipinos was relatively invariant across all levels of BMI, but was strongly inversely related to BMI in NHANES and exhibited only at the BMI>25 kg/m² threshold. Diet did not consistently predict the low-HDL phenotype in Filipinos. Filipino women exhibit a high prevalence of the isolated low HDL-c phenotype, which is largely decoupled from anthropometric factors. The relationship of CVD to population variation in dyslipidemia and body composition needs further study, particularly in populations where the burden of cardiovascular and metabolic disease is rapidly increasing.

Key Words: risk factors, dyslipidemia, low HDL-c, women, epidemiology

INTRODUCTION

Cardiovascular disease (CVD) is a leading cause of death in the Philippines,¹ where rates of heart disease exceed those found in many nations in Western Europe and throughout the Asia Pacific region.² In recent decades, the prevalence of obesity has risen in the Philippines and has likely contributed to these trends.³ However, mean body mass and waist circumference remain lower in the Philippines than in the United States and Western Europe, and intake of dietary fat and incidence of lifestyle factors implicated in adverse cardiovascular health are lower as well, hinting at possible environmental and biological differences in the etiologic pathways that lead to CVD in the Philippines. The need to understand population differences in susceptibility is underscored by evidence that body mass index (BMI) cut-points for overweight, obesity, and CVD risk based on Western populations may inadequately screen some Asian populations,^{4,5} which

may have elevated CVD risk at lower levels of relative weight.

In the Philippines, we have previously shown that adolescent males and females with low BMI, low fat intake, and relatively high levels of physical activity have notably high levels of atherogenic risk as indicated by lipid profiles, with low high density lipoprotein cholesterol (HDL-c) and a corresponding high ratio of total cholesterol or low density lipoprotein cholesterol (LDL-c) to HDL-c being common.⁶ Past studies of Filipinos have

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similarly found low HDL-c in adult males and boys.^{7,8} The Food and Nutrition Research Institute of the Philippines recently reported that the mean HDL-c in the National Nutrition and Health Survey (NNHes), a nationally representative survey of adults, was 41.4 mg/dL, and the prevalence of HDL-c <40 mg/dL was 50%.⁹ Further, Filipino women residing in the United States were also found to have lower HDL-c, higher triglycerides, and a higher total cholesterol/HDL-c ratio than white women.¹⁰

The prevalence of dyslipidemias has been found to differ across populations.¹¹⁻¹³ An isolated low HDL-c phenotype is one in which HDL-c is low (<35 mg/dL), but triglycerides are normal (<200 mg/dL), whereas hypertriglyceridemia combines HDL-c<35 mg/dL with triglycerides>200 mg/dL.¹¹ The isolated low HDL-c phenotype has been described in several non-European populations where CVD risk is high (Mexico,¹¹ India,¹⁴ Iran,¹⁵ Turkey,¹⁶ Thailand).¹³ Low HDL-c is an important independent risk factor for CVD^{17,18} suggesting that a distinct low HDL-c phenotype may be related to population variation in CVD risk even when total cholesterol is not elevated or BMI levels are defined as normal.

Although previous findings suggest that individuals of Filipino descent exhibit low HDL-c and elevated triglycerides,^{6-9,19} to our knowledge no previous study has applied clinical definitions of dyslipidemic phenotypes to any Filipino population. Here, we describe lipid profiles in a sample of adult women, aged 35-69, living in Cebu, Philippines, whom we compare to US women of the same age participating in the 2005-06 National Health and Nutrition Examination Survey (NHANES). Specifically, we evaluate whether individual lipid risk factors relate differently to common body composition measures in the two samples and whether women from the Philippines exhibit lipid phenotypes distinct from those observed in the US.

MATERIALS AND METHODS

Participants and data collection in the Philippines

The Cebu Longitudinal Health and Nutrition Survey (CLHNS) began in 1983 with the recruitment of 3,327 pregnant women from Cebu City. These women comprised a random sample and were representative of the national population. The women have been followed through multiple rounds of data collection since 1983. Data for the current analyses of serum lipid concentrations come from 2005, when blood was collected for lipid analysis. Lipid analysis was conducted on blood samples from 1,896 women ranging in age from 35-69 years old. Of those women, complete anthropometric and nutritional data were available for 1,877. Height, weight, and waist circumference were measured using standard anthropometric techniques.²⁰ A dummy variable was constructed to identify women taking statins. All data were collected under conditions of informed consent with institutional review board approval from the University of North Carolina, Chapel Hill.

Diet variables were assessed by two 24-hour dietary recalls. A local conversion table was developed to convert portion sizes (e.g., one cup) to weight equivalents in grams.²¹ Energy and nutrient intakes were calculated using the Philippines Food Composition Tables produced by the Food and Nutrition Research Institute of the Phil-

ippines²² and values were entered into a database. Total calories from fat were calculated by multiplying fat grams consumed by 9; a multiple of 4 was used to calculate carbohydrate calories. Calories and dietary component percentages (macronutrient calories/total calories*100) were averaged across the two days of recall. The data presented are total daily calories, percentage of calories from fat, and percentage of calories from carbohydrates. We focused on these two macronutrients because of their emphasis in the literature on cardiovascular disease risk. Inter-observer reliability was periodically assessed during the data collection period.²³ Total caloric intake was evaluated as kilocalories/1000 to create larger units for ease of interpretation of coefficients in regression models.

We evaluated how our sample differed from the original cohort as assessed when the study started in 1983. Compared to those lost to follow up, participants remaining in this study did not differ in any income, weight, or BMI, but were significantly older (by an average difference of 1.19 years) and had significantly smaller waist circumferences (by an average difference of 1.96 cm).

Lipid analysis (Philippines)

In Cebu, participants were asked to fast overnight for 12 hours, and blood samples were collected in clinics the following morning using EDTA-coated tubes. After separation, plasma samples were frozen and shipped on dry ice to the Emory Lipid Research Laboratory (Atlanta, GA) for analysis of lipid profiles. All samples remained frozen at -80°C until ready for analysis. Total lipids were determined by enzymatic methods using reagents from Beckman Diagnostics (Palo Alto, CA) on a CX5 chemistry analyzer. HDL-cholesterol was determined using the homogenous assay direct HDL-c (Genzyme Corporation, Exton, PA). LDL-cholesterol was determined using the Friedewald calculation. The Emory Lipid Research Laboratory is a participant in the CDC/NHLBI Lipid Standardization Program to ensure accuracy and precision of the determinations.

Comparisons with NHANES

In 1999, NHANES converted from a periodic sampling schedule to a continuous annual survey, released in two year increments. For the current analyses, data collected in 2005-2006 were used to better match the sampling period in Cebu. Because NHANES uses a complex sampling strategy to over-represent specific demographic subgroups, probability sample weights were used with "svy" commands in Stata to correct for sample design in analyses presented here. The sample weight used is that which corresponds to the smallest number of variables held in common by all individuals within a sample; in this case, the weight applied was "wtsaf2yr." The NHANES sampling weights account for unequal probabilities of selection, non-response adjustments, clustering, and stratification, and thus the application of weights correct for sampling design to recreate samples that are representative of the US population. To maximize comparability with the Cebu sample, all adult females aged 35-69 years and with all available anthropometric and laboratory measurements (n=477) were selected for the current

analysis. We constructed a dummy variable to identify statin-users in the NHANES sample.

Detailed documentation regarding data collection and lipid analysis for NHANES can be found on the NHANES website.²⁴⁻²⁷ Briefly, blood samples from participants were analyzed at Johns Hopkins Hospital, Baltimore, MD. Total cholesterol and triglycerides were measured enzymatically using the Hitachi 717 (2005 and 2006) and Hitachi 912 (2006).^{25,26} HDL-c was determined directly by the Roche/Boehringer-Mannheim Diagnostics method on the Hitachi 717 (2005 and 2006) and Hitachi 912 (2006).²⁴ LDL-c was calculated using the Friedewald calculation.²⁸ Anthropometric data were collected according to standard procedures.²⁰ Diet variables were collected via two-day dietary recalls, and calories and dietary component percentages were averaged across the two days. NHANES is conducted under conditions of informed consent and institutional review board oversight.

Definition of lipid phenotypes

Following Aguilar Salinas *et al.*¹¹ individuals were classified as having the isolated low HDL-c phenotype if their HDL-c was less than 35 mg/dL but with normal triglycerides (i.e., <200 mg/dL). Hyperlipidemia was defined as a combination of HDL-c <35 mg/dL and triglycerides >200 mg/dL. Severe dyslipidemia was defined as triglycerides >500 mg/dL and/or total cholesterol >300 mg/dL.

Body composition categories

Recent literature suggests that BMI cut-offs that are derived from Western populations defining a BMI of 25 kg/m² as the threshold for overweight and CVD risk may not be appropriate for individuals of Asian descent, who appear to be susceptible to cardiovascular and metabolic disease at lower levels of relative weight.^{4,29,30} A recent analysis by the World Health Organization suggests that in addition to traditional definitions of 25 kg/m² as overweight and 30 kg/m² as obese, a BMI of 23 kg/m² should be considered a potential public health action point for Asian populations.³¹ Therefore, we defined our categories using the WHO International Classification of BMI, with cut-offs at <18.5 kg/m² (underweight), 18.5-22.99 kg/m² (normal), 23-24.99 kg/m² (public health action point), 25-29.99 kg/m² (overweight), and ≥30 (obese) kg/m².³¹

Statistical analysis

Means and standard errors were calculated for each study sample separately, with the appropriate probability sampling weight applied to the NHANES sample. T-tests were performed using these separately calculated values to compare the two samples in Table 1. Because it was not necessary to apply sampling weights to the Cebu sample, data from the two surveys were never combined into single regression models. Rather, linear regression models were performed in Stata separately for each sample to determine the relationship between directly measured lipid components (total cholesterol, triglycerides, and HDL-c) and anthropometric and dietary variables. Because early models in both samples indicated significant effects of interactions between age and BMI on some of the lipid components, all subsequent models were stratified on two age categories, based on within-sample median splits (NHANES=50 years, CLHNS=47.67 years). Logistic regression was then used to evaluate the anthropometric and other predictors of each lipid phenotype for each sample separately.

RESULTS

Table 1 reports descriptive statistics for women in the US and Cebu. Women in the Philippines were shorter, lighter, and thinner than the US women. Although the same age range was used in the two study samples, mean age was higher in the US, reflecting fewer women in the older age categories in the Philippines. Filipino women consumed fewer calories and the proportion of calories from fat was significantly lower, while the proportion of carbohydrate calories was about 40% higher than in the US. Mean total cholesterol was significantly lower in women from Cebu. However, Cebu women had marginally higher LDL-c and triglycerides. In contrast, mean HDL-c was roughly 33% lower in women from Cebu than in women from the US and the ratio of total cholesterol to HDL-c was 37% higher in Cebu than in the US.

Next, we ran a series of linear regression models to evaluate relationships between individual lipid concentrations and anthropometric and dietary variables in the two samples. In Cebu, age and BMI were significant predictors of cholesterol across both age groups (Table 2). For older women, total caloric intake and higher percentage

Table 1. Descriptive statistics for Cebu and US women

	Cebu (n=1877)	NHANES (n=477)	t-value	s.e. of difference	p value
	Mean (s.e.)	Mean (s.e.)			
Age (yrs)	48.5 (0.14)	51.2 (0.46)	7.46	0.36	<0.0001
Weight (kg)	55.1 (0.25)	79.1 (0.96)	34.6	0.69	<0.0001
Height (cm)	150.6 (0.12)	161.8 (0.29)	40.1	0.28	<0.0001
BMI (kg/m ²)	24.3 (0.10)	30.2 (0.36)	21.9	0.27	<0.0001
Waist circumference (cm)	81.1 (0.25)	97.7 (0.76)	26.5	0.63	<0.0001
Daily calories, total (kcal)	1138.6 (11.5)	1714.8 (27.7)	21.5	26.7	<0.0001
Daily calories from fat (%)	15.0 (0.00)	33.9 (0.35)	107.2	0.18	<0.0001
Daily calories from carbohydrates (%)	68.8 (0.28)	49.3 (0.42)	32.8	0.59	<0.0001
Statin use (%)	0.16 (0.09)	15.8 (1.67)	15.2	1.03	<0.0001
Total cholesterol (mg/dL)	186.5 (0.90)	203.1 (1.97)	8.1	2.04	<0.0001
HDL-c (mg/dL)	40.8 (0.24)	60.7 (0.74)	32.9	0.61	<0.0001
Total chol/HDLC ratio	4.8 (0.03)	3.5 (0.05)	20.1	0.07	<0.0001
LDL-c (mg/dL)	119.3 (0.78)	117.5 (1.72)	1.0	1.77	0.31
Triglycerides (mg/dL)	130.7 (1.96)	124.1 (2.97)	1.6	4.17	0.11

Table 2. Multiple regression models predicting cholesterol in Cebu and US women, stratified by age[†]

CHOLESTEROL	Model 1: Cebu		Model 2: United States [‡]	
	Younger women n=940 β (95% C.I.)	Older women n=937 β (95% C.I.)	Younger women n=223 β (95% C.I.)	Older women n=254 β (95% C.I.)
Age (years)	1.42*** (0.57, 2.27)	0.56* (-0.02, 1.13)	0.16 (-1.11, 1.43)	0.05 (-0.87, 0.98)
BMI (kg/m ²)	1.77***** (1.23, 2.30)	2.26***** (1.66, 2.85)	0.10 (-0.64, 0.84)	-0.62* (-1.30, 0.06)
Kilocalories/1000	3.95 (-1.04, 8.94)	6.22** (-0.01, 12.45)	1.12 (-7.21, 9.45)	1.84 (-8.64, 12.31)
% fat calories	0.35 (-0.19, 0.88)	0.69** (0.08, 1.31)	-0.58 (-1.57, 0.41)	0.99* (-0.15, 2.12)
% carbohydrate calories	0.06 (-0.41, 0.53)	0.23 (-0.29, 0.75)	-0.65 (-1.48, 0.17)	0.62 (-0.32, 1.54)
Statin use	-17.30 (-85.40, 50.80)	-14.82 (-68.96, 39.32)	-22.20* (-47.68, 3.28)	-2.96 (-15.29, 9.37)
Constant	60.01* (3.60, 116.4)	77.31* (20.89, 133.74)	234.51***** (143.82, 325.21)	161.56***** (68.15, 254.98)
Model R ²	0.078	0.105	0.026	0.026

[†]Age groups determined by within-population median split: Cebu, 47.67 years; US, 50 years

[‡]NHANES data weighted

***** $p < 0.0001$, **** $p < 0.001$, *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$

Table 3. Multiple regression models predicting Triglycerides in Cebu and US women, stratified by age[†]

Triglycerides	Model 1: Cebu		Model 2: United States [‡]	
	Younger women n=940 β (95% C.I.)	Older women n=937 β (95% C.I.)	Younger women n=223 β (95% C.I.)	Older women n=254 β (95% C.I.)
Age (years)	1.01 (-0.63, 2.65)	1.13 (-0.27, 2.53)	-1.51 (-3.46, 0.43)	0.94 (-0.40, 2.27)
BMI (kg/m ²)	4.07***** (3.05, 5.10)	4.18***** (2.73, 5.64)	1.70*** (0.57, 2.83)	1.01** (0.03, 1.99)
Kilocalories/1000	-4.22 (-13.86, 5.40)	6.25 (-8.90, 21.40)	11.95* (-0.79, 24.68)	1.56 (-13.58, 16.70)
% fat calories	0.34 (-0.69, 1.38)	0.49 (-1.01, 1.98)	-1.53** (-3.04, -0.02)	1.08 (-0.56, 2.72)
% carbohydrate calories	-0.19 (-1.09, 0.72)	-0.10 (-1.37, 1.17)	0.30 (-0.95, 1.56)	1.56** (0.21, 2.90)
Statin use	-60.43 (-191.78, 70.93)	110.53* (-21.08, 242.13)	14.81 (-24.15, 53.77)	10.73 (-7.10, 28.55)
Constant	-13.93 (-122.72, 94.86)	-23.49 (-160.65, 113.66)	143.05 (4.37, 281.73)	-73.81** (-208.85, 61.22)
Model R ²	0.073	0.054	0.109	0.058

[†]Age groups determined by within-population median split: Cebu, 47.67 years; US, 50 years

[‡]NHANES data weighted

***** $p < 0.0001$, **** $p < 0.001$, *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$

of dietary fat were both positively associated with cholesterol concentrations. In the US, BMI and % calories from fat were only weakly associated with cholesterol in the older women, with the relationship between BMI and cholesterol being negative. Overall, the models explained more variation in cholesterol concentrations in Cebu than they did in the US (7.8-10.5% vs. 2.6%, respectively).

Body mass index was a strong predictor of triglycerides across both age groups in Cebu and also in NHANES (Table 3). Among younger US women, total calories were positively related to triglycerides, whereas % calories from carbohydrates inversely predicted triglycerides in older women. The models explained comparable levels of variation in log triglycerides across

both populations (5.4-7.3% in Cebu vs. 5.8-10.9% in the US).

Body mass index and the proportion of calories from carbohydrates were significantly inversely associated with HDL-c among the younger age stratum at Cebu, while total caloric intake was a positive predictor of HDL-c. These relationships were not present in the older Cebu women (Table 4). In the US sample, BMI and % calories from carbohydrates were also significant positive predictors of HDL-c concentration for all women, with relative fat intake emerging as a predictor among older women only. The final models explained far less of the variation in HDL-c concentrations in Cebu than in the US (2.2-3.2% vs. 9.1-21.9%, respectively).

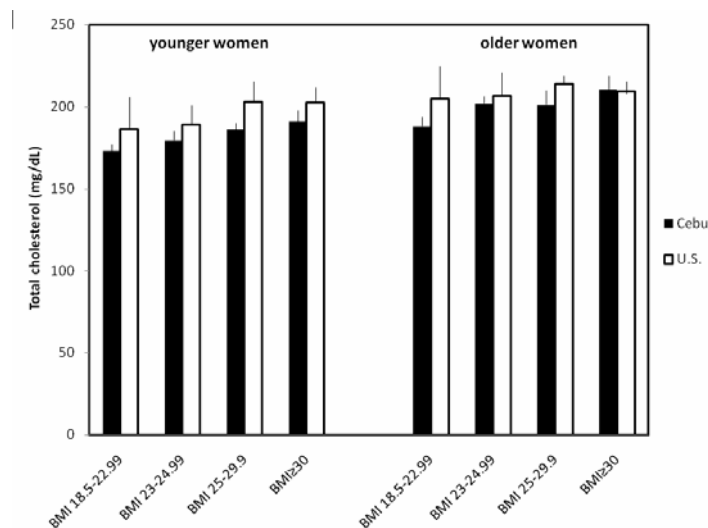
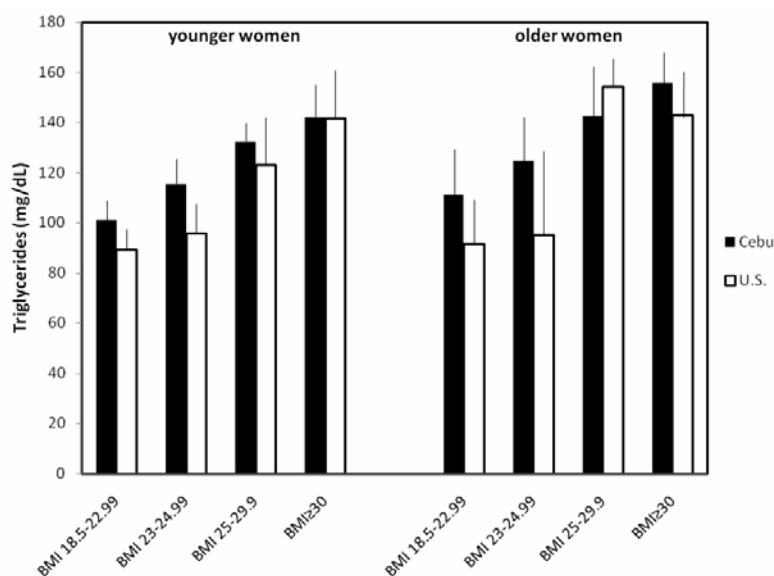
Table 4. Multiple regression models predicting HDL-c in Cebu and US women, stratified by age[†]

HDL-c	Model 1: Cebu		Model 2: United States [‡]	
	Younger women n=940	Older women n=937	Younger women n=223	Older women n=254
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Age (years)	0.007 (-0.24, 0.25)	0.03 (-0.12, 0.18)	0.35 (-0.13, 0.83)	0.02 (-0.30, 0.33)
BMI (kg/m ²)	-0.22*** (-0.38, -0.07)	-0.08 (-0.24, 0.08)	-0.92***** (-1.20, -0.65)	-0.31*** (-0.55, -0.08)
Kilocalories/1000	1.64** (0.19, 3.09)	0.75 (-0.91, 2.40)	1.28 (-1.86, 4.41)	1.59 (-1.99, 5.17)
% fat calories	-0.07 (-0.22, 0.09)	0.12 (-0.04, 0.29)	-0.026 (-0.40, 0.35)	-0.39** (-0.78, -0.01)
% carbohydrate calories	-0.15** (-0.29, -0.02)	-0.002 (-0.14, 0.14)	-0.39** (-0.70, -0.08)	-0.61***** (-0.93, -0.29)
Statin use	1.20 (-18.58, 20.97)	-10.35 (-24.72, 4.01)	-3.65 (-13.23, 5.94)	0.49 (-3.73, 4.70)
Constant	56.21***** (39.83, 75.59)	37.99***** (23.01, 52.96)	91.09 (56.98, 125.21)	110.10***** (78.17, 142.02)
Model R ²	0.032	0.022	0.219	0.091

[†]Age groups determined by within-population median split: Cebu, 47.67 years; US, 50 years

[‡]NHANES data weighted

***** $p \leq 0.0001$, *** $p \leq 0.001$, ** $p \leq 0.01$, * $p \leq 0.05$, $p \leq 0.10$

**Figure 1a.** Total cholesterol (mg/dL) across increasing categories of BMI (kg/m²) in younger and older women in the Philippines and NHANES.**Figure 1b.** Triglycerides (mg/dL) across increasing categories of BMI (kg/m²) in younger and older women in the Philippines and NHANES.

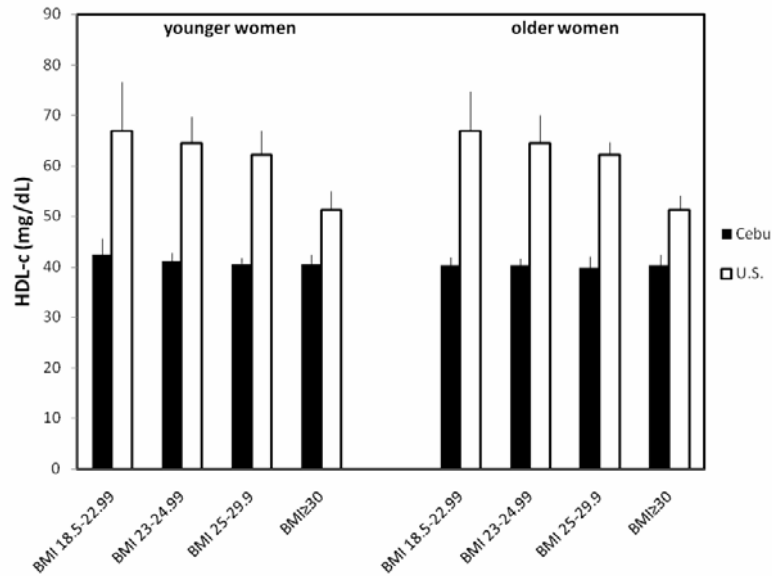


Figure 1c. HDL-c (mg/dL) across increasing categories of BMI (kg/m²) in younger and older women in the Philippines and NHANES.

Table 5. Prevalence (%) of different abnormal lipid phenotypes in women from Cebu, Philippines and the U.S. by categories of body mass index

BMI (kg/m ²)	Low HDL-c/ normotriglyceridemia		Hyperlipidemia		Severe dyslipidemia	
	Cebu	NHANES	Cebu	NHANES	Cebu	NHANES
<18.5	29.94	0	0.87	0	0	0
18.5-22.99	27.85	0	4.47	0	1.01	1.49
23-24.99	29.67	0	8.04	0	2.67	1.54
25-29.99	28.17	2.40	10.24	1.94	1.17	2.40
≥30	31.07	3.30	11.21	1.18	2.26	3.30
All women	28.77	2.10	7.30	0.99	1.39	2.52
	(13.7x greater in Cebu)		(7.37x greater in Cebu)		(1.81x greater in the US)	

Low HDL-c /normotriglyceridemic: HDL-c <35 mg/dL and triglycerides <200; Hyperlipidemia: triglycerides >200 mg/dL and HDL-c <35 mg/dL; Severe dyslipidemia: combination of triglycerides >500 mg/dL and/or cholesterol >300 mg/dL.

Table 6. Multiple logistic regression models predicting presence of the isolated low- HDL-c phenotype, stratified by age[†]

	Model 1: Cebu		Model 2: United States [‡]	
	Younger women n=940	Older women n=937	Younger women n=223	Older women n=254
	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
Age (years)	0.98 (0.93, 1.04)	0.98 (0.95, 1.02)	0.94 (0.81, 1.10)	1.19 (1.03, 1.39)**
BMI (kg/m ²)	1.02 (0.99, 1.06)	1.01 (0.97, 1.04)	1.08 (0.99, 1.18)*	1.00 (0.95, 1.06)
Kilocalories/1000	0.82 (0.58, 1.15)	0.91 (0.63, 1.29)	0.80 (0.25, 2.59)	0.45 (0.14, 1.38)*
% fat calories	1.03 (1.00, 1.07)*	0.98 (0.94, 1.01)	0.89 (0.77, 1.03)*	0.89 (0.84, 0.94)*****
% carbohydrate calories	1.04 (1.01, 1.08)**	0.99 (0.96, 1.02)	1.10 (0.95, 1.27)	0.90 (0.82, 0.99)**

[†]Age groups determined by within-population median split: Cebu, 47.67 years; US, 50 years

[‡]NHANES data weighted

******p*<0.0001, *****p*<0.001, ****p*<0.01, ***p*<0.05, **p*<0.10

Next, we investigated the relationship between BMI and individual lipid components in Cebu and NHANES. In both samples, total cholesterol and triglycerides were higher at higher levels of BMI (Figure 1a-b). The relationship between HDL-c and body composition measures was markedly different in the two samples: HDL-c was

clearly inversely related to BMI in women from the US but remained uniformly low at all levels of BMI in women from the Philippines (Figure 1c).

We next evaluated the prevalence of three dyslipidemic phenotypes in the two samples (Table 5). The prevalence of the isolated low HDL-c phenotype was

28.77% in the Filipino women, compared to only 2.10% in the US women. The prevalence of this phenotype increased as BMI increased in the US sample, although it remained at relatively low levels across the entire BMI range. There were no reported examples of this phenotype among women in NHANES with BMI <25 kg/m². In contrast, prevalence of the low-HDL phenotype in Cebu was high at all levels of BMI, even among those women categorized as underweight, and did not increase appreciably at higher levels of BMI. Prevalence of hypertriglyceridemia was also higher in the Cebu sample (7.3%) than in the US (0.99%). In contrast, the prevalence of severe dyslipidemia, marked by very high levels of triglycerides and high cholesterol, alone or in combination, was similarly low in both samples.

In light of the high prevalence of the isolated low HDL-c phenotype in Cebu, we next used logistic regression models to evaluate the factors that predict the presence of this phenotype in Cebu and NHANES (Table 6). In Cebu, neither BMI nor total caloric intake predicted the phenotype, nor was age a factor. Among women in the younger age stratum at Cebu, each % increase in carbohydrate calories was associated with a 4% increase in risk of the low HDL-c phenotype. Percent calories from fat were a marginally positive predictor of the phenotype among the younger Cebu women. In the older women in NHANES, each additional year of age predicted a 19% increase in the risk of having the isolated low HDL-c phenotype. Among the younger US women each unit increase in BMI was associated with an 8% increase in the probability of exhibiting the phenotype. In contrast to the Cebu women, each percentage increase in fat and carbohydrate calories was associated with a significant drop (11% and 10%, respectively) in the risk of having the phenotype in older US women.

DISCUSSION

Women from Cebu, Philippines had marginally higher LDL-c and triglycerides and significantly lower HDL-c at all levels of BMI compared to women from the US. The mean HDL-c value for all women (40.8 mg/dL) in the Cebu sample was well below the cut-off used as one of the diagnostic characteristics of the metabolic syndrome in women (50 mg/dL).^{32,33} This lipid profile is striking because Cebu women were also lighter, shorter, and thinner than women from the US. They also consumed fewer calories, a significantly smaller percentage of which were derived from fat, and had significantly lower total cholesterol. Despite their apparent lower risk profile (e.g., BMI, dietary variables), our findings confirm that women from Cebu exhibit a distinct isolated low HDL-c phenotype compared to a well-characterized US sample.

The prevalence of a clinically-defined isolated low high-density lipoprotein phenotype was over 13 times greater in women from the Philippines compared to women from the US; nearly 70% of the women had HDL-c concentrations <45 mg/dL. Our findings are similar to those reported in the National Nutrition Health Survey conducted by the Philippines government in which 64.5% of women over the age of 20 had HDL-c <45 mg/dL, with a mean of 42.6 mg/dL.⁹ This prevalence is also higher than the 56.3% reported by a study of Iranian

women.¹⁵ The prevalence of the low HDL-c phenotype reported in the Philippines is among the highest reported, and is nearly identical to the 28.7% reported among Mexican women.¹¹ In comparison, only 14.4% of women from the US in this study had HDL-c <45 mg/dL and only 2.10% fell within the clinical definition of the isolated low HDL-c phenotype, suggesting significant population variation in this lipid characteristic. The prevalence of a hypertriglyceridemic phenotype was also considerably higher in the Philippines than in the US sample (7.3% vs 0.99%, respectively), which is in large part due to the high prevalence of low HDL-c among Filipinos.

We demonstrated previously that 38.8% of the adolescent daughters (14-16 years) of the women described in the current study had HDL-c <45 mg/dL.⁶ In these offspring, 32.5% exhibit the isolated low HDL-c phenotype despite low average BMI and fat intake (Kuzawa et al, unpublished analysis). In Cebu, BMI, total caloric intake, and relative carbohydrate intake all predicted decreased HDL-c in younger but not older women. Similarly, increased fat and carbohydrate consumption predicted increased risk of the low HDL-c phenotype in younger women only. Our dietary estimates are based on two 24-hour dietary recalls, and thus are relatively low resolution measures of individual intake. Although awaiting verification with improved dietary assessments, our findings suggest that diet and anthropometry may have greater influence on lipid profiles among younger Filipino women in the Philippines, suggesting that they could reap long-term benefits from changes in diet and lifestyle.

BMI was an important predictor of the low HDL-c phenotype in the US women, but not in the women from Cebu, and only HDL-c showed an absence of variation across categories of increasing BMI in Cebu. Recent studies have demonstrated that BMI cut-offs derived from Western populations and used to identify CVD risk may be inappropriate for Asian populations.^{29,30} For example, a study of Thai adults showed that risk of atherogenic lipoprotein profiles, including low HDL-c, increased above a BMI of ≥ 23 kg/m².⁴ The pattern we report here of low HDL-c even in individuals in the Philippines with BMI <18.5 kg/m² reinforces the observation that at least for low HDL-c, screening based on US BMI thresholds (e.g., 25 kg/m²) may miss a large segment of the Filipino population at potential risk of CVD.

The causes of isolated low HDL-c remain poorly understood, but could include some combination of nutritional, developmental and/or genetic factors. Women from Cebu acquire a significantly greater proportion of their caloric intake from carbohydrates than do US women (68.8% vs. 49.3%, respectively), largely in the form of rice products, and it has been suggested that high consumption of simple carbohydrates may contribute to the prevalence of low HDL-c phenotypes.³⁴ A study of a multi-ethnic Canadian sample (South Asian, Aboriginal, Chinese, and European origins) found that HDL-c was highest for adults in the lowest tertile of carbohydrate intake.³⁵ However, in the current study the effect of carbohydrates in the Filipino diet on HDL-c was equivocal, being a significant predictor of elevated risk of the low HDL-c phenotype in younger but not older women. In contrast, increased carbohydrate consumption was a pre-

dictor of reduced risk of low HDL-c phenotype among older women in the NHANES sample, suggesting that dietary factors, possibly as a result of differences in food sources and agricultural procedures, may play different roles in the etiology of low HDL-c across different populations. It could also reflect that carbohydrate intake in the US is either not at a high enough threshold to contribute to increased risk, or represents greater intake of complex carbohydrates which may be protective against low HDL-c concentrations.^{36,37} More refined data than are currently available are required to resolve this issue.

The low HDL-c phenotype in the Cebu women could also indicate a role for HDL-suppressing genetic polymorphisms. Several genes have been cited as potential candidates for a low-HDL genotype,³⁸ including ABCA1^{39,40} and the TaqIB polymorphism of the cholesterol ester transfer protein (CETP).⁴¹⁻⁴³ At present, the prevalence of genetic variants related to low HDL-c in the Philippines remains unknown although a recent study did report an association between CETP polymorphisms and HDL-c concentrations among adult Filipinos.¹⁹ It will be important for future work to explore population differences in prevalence of these and other polymorphisms in association with lipid profiles.

It is not clear how much of an independent CVD risk low HDL-c poses in this Filipino sample. Although the primary target to decrease CVD risk is the lowering of LDL-c rather than the raising of HDL-c,⁴⁴ there is a large body of evidence suggesting that low HDL-c, even in isolation from other lipids, is an independent CVD risk factor.^{18,45,46} For example, a recent prospective Korean study found that adult males at the lowest quantile of HDL-c had an elevated risk of ischemic heart disease of 57% when HDL-c was considered in isolation, which was reduced to 33% when combined with elevated triglycerides.⁴⁶ Goldbourt *et al*¹⁸ report a similar level of prospective risk of cardiovascular events in association with isolated low HDL-c. Further, results from the Women's Health Study indicate that the risk of future cardiovascular events was positively predicted by the ratio of total cholesterol to HDL-c⁴⁷ which is commonly used as predictor of cardiovascular incidents and death.^{48,49} In the current study, this ratio is significantly higher in women from the Philippines compared to women from the US, strengthening the possibility of a role for HDL-c in the elevated risk of CVD in this region.^{1,2} Low HDL-c has recently been shown to be predictive of memory deficit and decline in older adults,⁵⁰ possibly through its role in brain cholesterol homeostasis,⁵¹ suggesting that this lipid characteristic may pose broader health risks in aging populations. Future research in the Philippines that evaluates the importance of isolated HDL-c as a predictor of incident CVD will be necessary to clarify the disease implications with certainty.

In sum, the Filipino women in our sample have lipid profiles that are distinct from those found in the US women. A key finding is a very high prevalence in Cebu women of the isolated low HDL-c phenotype, which is common across the entire range of BMI and only weakly related to dietary measures. The etiology of CVD relative to population variation in dyslipidemia and body composition needs further study, particularly in relatively under-

studied populations where the burden of cardiovascular and metabolic disease is rapidly increasing.

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AUTHOR DISCLOSURES

The authors report no conflicts of interest.

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Original Article

High prevalence of low HDL-c in the Philippines compared to the US: population differences in associations with diet and BMI

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菲律賓低的高密度脂蛋白膽固醇盛行率較美國高：其與飲食和身體質量指數的相關性有族群差異

在菲律賓，心血管疾病是主要死因，但很少研究檢測與疾病危險性相關的血脂質型態。高密度脂蛋白膽固醇較低的基因顯型已被認為是心血管疾病的獨立危險因子，而其盛行率在不同族群中呈現顯著的差異。為了檢測個體血脂組成在不同族群中的變異及其和飲食、體位測量間的相關性，我們比較菲律賓成年女性(1877位)和美國參予國家健康營養調查研究(NHANES)的女性(477位)。使用複迴歸模式來評估在兩個族群中，血脂質組成和身體質量指數、飲食因子之間的關係。估量血脂質顯型盛行率，及使用邏輯斯迴歸來決定低的高密度脂蛋白膽固醇顯型之預測因子。高密度脂蛋白膽固醇濃度在菲律賓女性(40.8±0.2 mg/dL)低於美國 NHANES 的女性(60.7±0.7 mg/dL)。菲律賓女性高密度脂蛋白膽固醇較低的顯型盛行率為 28.8%，在 NHANES 的女性則僅有 2.10%。菲律賓女性的高盛行率，在不同身體質量指數間變異不大；但在 NHANES 的女性中，盛行率在身體質量指數>25 kg/m²才顯現，且和身體質量指數有很強的負相關。在菲律賓女性，飲食不能一致地預測低的高密度脂蛋白膽固醇。總之，菲律賓女性表現出較高盛行率的高密度脂蛋白膽固醇低的顯型，此和體位的因子無相關。心血管疾病和血脂異常及體組成的關係在不同族群中的差異，需要更進一步的研究，尤其在心血管疾病及代謝性疾病快速增加的地區特別重要。

關鍵字：危險因子、血脂異常、低的高密度脂蛋白膽固醇、婦女、流行病學