American Journal of Preventive Cardiology 19 (2024) 100687

Contents lists available at ScienceDirect

American Journal of Preventive Cardiology

journal homepage: www.journals.elsevier.com/american-journal-of-preventive-cardiology

HDL-C criterion of the metabolic syndrome and future diabetes and atherosclerosis in midlife women: The SWAN Study☆,☆☆,★,★★

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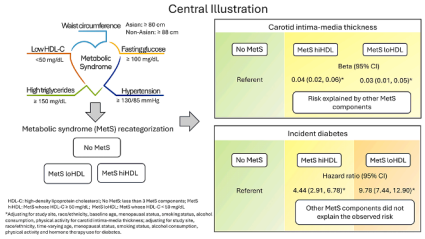
HIGHLIGHTS

- Midlife women with metabolic syndrome face an increased risk of developing incident diabetes and exhibit higher levels of subclinical measures of atherosclerosis independent of their HDL-C status.
- HDL-C classification contributes significantly to risk prediction of incident diabetes, beyond levels of other metabolic syndrome components in midlife women.
- Our findings underscored differential contributions of HDL-C in risk prediction for MetS on incident diabetes and subclinical atherosclerosis measures.

GRAPHICAL ABSTRACT



☆ Statement of authorship: Ziyuan Wang engaged in conceptualizing the analysis, conducted the analysis, wrote the original draft, and provided editing of the manuscript. Dr. Emma Barinas-Mitchell collected the data and offered review and editing of the manuscript. Dr. Maria Brooks serves as the principal investigator of the SWAN study and provided review and editing of the manuscript. Dr. Samar El Khoudary engaged in conceptualization of the analysis, supervised the analysis and the manuscript, and also provided review and editing. All other coauthors contributed to the review and editing of the manuscript.

☆☆ Funding: The Study of Women's Health Across the Nation (SWAN) has grant support from the National Institutes of Health (NIH), DHHS, through the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR) and the NIH Office of Research on Women's Health (ORWH) (Grants U01NR004061; U01AG012505, U01AG012535, U01AG012531, U01AG012539, U01AG012546, U01AG012553, U01AG012554, U01AG012495, and U19AG063720). The SWAN Repository (U01AG017719).

★ The Study of Women's Health Across the Nation (SWAN) HDL ancillary study has grant support from National Institute on Aging (NIA) AG058690.

★★ The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the NIA, NINR, ORWH or the NIH. Dr. Aleda Leis is additionally supported by training grant K12TR004374 and UM1TR004404.

Disclosure: Dr. Rebecca Thurston is a consultant and advisor for Astellas Pharma, consultant and received travel support from Bayer, and on the medical advisory board for Hello Therapeutics. All other coauthors have nothing to disclose.

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https://doi.org/10.1016/j.ajpc.2024.100687
Received 20 December 2023; Received in revised form 21 April 2024; Accepted 12 June 2024
Available online 19 June 2024

- Our results emphasized the importance of understanding the association between different components of metabolic syndrome and the risk of developing cardiometabolic events in midlife women, due to the high prevalence of metabolic syndrome in this population.
- Our findings also highlight the necessity of controlling for HDL-C levels as a primordial prevention strategy for midlife women at alleviated risk of developing future diabetes.

ARTICLE INFO

Keywords:
Metabolic syndrome
HDL-C
Subclinical atherosclerosis
Diabetes

ABSTRACT

Objective: High-density lipoprotein cholesterol (HDL-C) is one of 5 components [high blood pressure, glucose, triglycerides, waist circumference, low HDL-C], 3 of which, needed to diagnose metabolic syndrome (MetS). Evolving research shows that higher HDL-C is not necessarily cardioprotective in midlife women, supporting a need to re-evaluate HDL-C's contribution to risks related to MetS. We tested whether risk of future diabetes and higher carotid intima-media thickness (cIMT) differ by HDL-C status in midlife women diagnosed with MetS based on the other 4 components.

Methods: Midlife women were classified into 3 groups: 1) no MetS, 2) MetS with HDL-C $\geq$ 50 mg/dL (MetS hiHDL), and 3) MetS with HDL-C $<$ 50 mg/dL (MetS loHDL). cIMT was measured 13.8 $\pm$ 0.6 years post baseline. Incident diabetes was assessed yearly.

Results: Among 2773 women (1350 (48 %) of them had cIMT), 2383 (86 %) had no MetS, 117 (4 %) had MetS hiHDL, 273 (10 %) had MetS loHDL. Compared with no MetS, both MetS- hiHDL and loHDL groups had higher cIMT and diabetes risk. Risk of having high cIMT did not differ between MetS loHDL vs. hiHDL groups. Adjusting for levels of MetS criteria other than HDL-C at baseline explained the associations of each of the two MetS groups with cIMT. Conversely, after adjustment, associations of MetS hiHDL and MetS loHDL with incident diabetes persisted.

Conclusions: In midlife women, HDL-C status matters for predicting risk of incident diabetes but not higher cIMT beyond other MetS components.

1. Introduction

Higher levels of high-density lipoprotein cholesterol (HDL-C) have been associated with a lower risk of future cardiovascular diseases (CVD) [1]. However, studies have challenged this protective role in midlife women transitioning through menopause, a period of adverse changes in lipids and lipoproteins [2,3],. Despite the ongoing debates of the clinical utility of HDL-C, current risk prediction equations [4-6] and clinical diagnosis of conditions, such as the metabolic syndrome (MetS), include level of HDL-C as a critical component. As such, re-evaluating the contribution of HDL-C in risk estimation among midlife women is pivotal.

MetS is a condition that is defined by the presence of at least three of the following five criteria: high blood pressure, high blood sugar, visceral obesity, low HDL-C and high triglycerides [7]. As women transition through menopause, their risk of developing MetS sharply increases [8,9] and the associations between their HDL-C levels and CVD risk is flipped [10]. As such, evaluating the cardiovascular risk associated with presence of MetS independent of HDL-C status (e.g., based on presence of criteria other than low HDL-C) is important in midlife women. Carotid intima-media thickness (cIMT) is a subclinical measure of arterial structural changes that may reflect the degree of atherosclerosis or vascular aging [11]. Cross-sectional and longitudinal studies have found that MetS is significantly associated with the progression of carotid atherosclerosis among midlife populations [12-14] and specifically among midlife women [15-17], supporting MetS as a risk factor for subclinical atherosclerosis. Moreover, the presence of MetS without diabetes is also highly predictive of future type 2 diabetes in the general population and among midlife women [18].

However, none of the above studies have examined the contribution of HDL-C to the predictive value of MetS for identifying women at elevated cardiometabolic risk. Therefore, the current study used prospective data from the Study of Women's Health Across the Nation (SWAN) study to understand the contribution of HDL-C classification independent of other diagnostic criteria of the metabolic syndrome to the risk of future incident diabetes and subclinical atherosclerosis among midlife women transitioning through menopause. We hypothesized that risk of future diabetes and higher carotid intima-media thickness (cIMT) differ by HDL-C status in midlife women diagnosed with MetS based on the other 4 components.

2. Methods

2.1. Study participants

The Study of Women's Health Across the Nation (SWAN) is an ongoing, multi-center, multi-ethnic longitudinal study aimed at characterizing both physiological and psychological changes during the menopause transition in women. The complete design of the SWAN study was published previously [19]. Briefly, the study recruited a total of 3302 women at seven clinical sites (Boston, Chicago, the Detroit area, Los Angeles, Newark, Pittsburgh, and Oakland California) between 1996 and 1997. At the time of enrollment, the women were between 42 and 52 years old and premenopausal. The recruited participants had an intact uterus and at least one ovary, were not pregnant or lactating at the recruitment time, and had not used hormone therapy for at least 3 months before recruitment. Participants self-identified as African American (28 %), Caucasian (47 %), Chinese (8 %), Hispanic (8 %), or Japanese (9 %).

Of the 3302 SWAN participants, 231 were excluded due to missing any MetS components (10 % with missing HDL-C, 78 % with missing glucose, 83 % with missing triglycerides, 15 % with missing waist

circumference and 3 % with missing hypertension status) at baseline SWAN visit. Furthermore, women diagnosed with MetS ($n = 298$) with three components, including low HDL-C, were excluded to enable studying the contribution of HDL-C classification on top of MetS diagnosed based on the other 4 criteria. Out of the remaining 2773 women, 1317 women had cIMT measured at visit 12 or 13 and contributed to analysis of cIMT. For the analysis focused on the incident diabetes, a total of 133 women out of 2773 women diagnosed with diabetes at baseline SWAN visit and were excluded, resulting in a total of 2640 women for the incident diabetes analysis between baseline visit and visit 16, Fig. 1.

The study protocol was approved by the institutional review board at each site, and all participants signed informed consent forms before entering the study.

2.2. Carotid intima-media thickness

cIMT measurements were obtained at visit 12 or visit 13 using Terason t3000 Ultrasound System (Teratech Corp, MA) equipped with a frequency 5–12 Mhz linear array transducer. Image data were collected by centrally trained sonographers and were streamed to the Ultrasound Research Laboratory, University of Pittsburgh for centralized reading. The semi-automated edge detection system developed in Sweden by Dr. Thomas Gustavsson [20] was used for reading. Specifically, images were taken from the left and right distal common carotid artery (CCA), which was 1 cm proximal to the carotid bulb). For each location, electronically traced data were collected from the lumen-intima interface and the media adventitia interface across a 1-cm segment of the near and far walls of the right and left distal CCA, resulting in approximately 140 data points per location. These readings were averaged within each location and then across all four locations to obtain the average cIMT value. Reproducibility of cIMT measures was excellent, with the intraclass correlation coefficient between sonographers being > 0.77, and the intraclass correlation coefficient between readers being > 0.89.

2.3. Diabetes ascertainment

Participants who reported the use of anti-diabetic medication at SWAN follow-up visit 1–16, had a fasting glucose level of $\geq$ 126 mg/dL on at least two of the three attended visits or on two consecutive visits, and had at least one visit with self-reported diabetes and a fasting glucose level of $\geq$ 126 mg/dL on at least one visit were classified as having incident diabetes.

2.4. Metabolic syndrome

Using the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) diagnostic criteria [21], women were diagnosed with MetS if they presented with at least three of the five criteria: abdominal obesity (defined as waist circumference$\geq$80 cm for Japanese/Chinese women, and$\geq$88 cm for others), hypertriglyceridemia (fasting triglycerides $\geq$150 mg/dL), low HDL-C (<50 mg/dL), impaired fasting glucose (fasting glucose$\geq$100 mg/dL or antidiabetic medication use), and hypertension (defined as systolic blood pressure$\geq$130 mmHg or diastolic blood pressure$\geq$85 mmHg or taking any blood pressure medication).

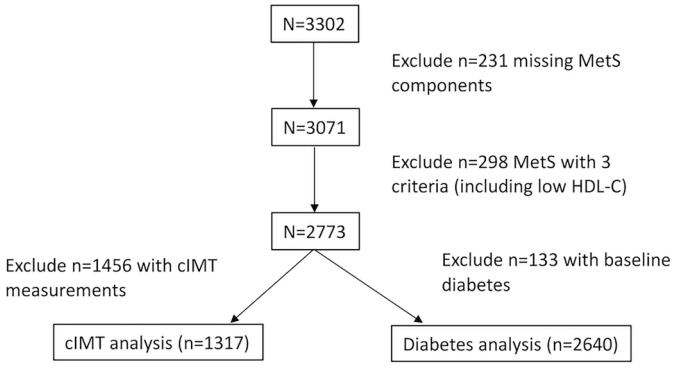

Fig. 1. Sample selection criteria for cIMT and diabetes analysis.

Measurement of the MetS components: MetS components were continuously measured throughout the SWAN study. Participants fasted overnight for at least 10 h prior to their blood draws. Fasting triglycerides were measured using the Hitachi 747–200 clinical analyzer at Medical Research Lab (MRL) in Lexington, KY at SWAN baseline, visit 1 and visits 3–7. Alternatively, the ADVIA assay was used at the University of Michigan (UM) in Ann Arbor, MI at SWAN visits 9 and 12. HDL-C was measured using EDTA-treated plasma at MRL at SWAN baseline, visit 1 and follow-up visits 3–7. For SWAN visits 9 and 12, HDL-C was analyzed using the ADVIA Direct-HDL Cholesterol method at UM. Fasting glucose was measured at MRL for SWAN baseline, visit 1 and visits 3–7 using an automated enzymatic assay on a Hitachi 747–200 chemistry analyzer with Roche Diagnostic's reagents and the hexokinase reaction. For SWAN visits 9, 12, 13, and 15, fasting glucose was analyzed using the ADVIA Chemistry Glucose Hexokinase-3 concentrated Reagents at UM. Due to changes in the labs for measurements, results analyzed at UM were calibrated to match those from MRL.

Blood pressure was measured on the right arms, with participants seated and feet flat on the floor for at least 5 min prior to measurements, and participants were required not to smoke or consume any caffeinated drinks within 30 min of the measurements. Two measurements, with two minutes rest period in between, were taken for each participant using a standard sphygmomanometer at the first Korotkoff sound. The average values of the two measures were used. Waist circumference was measured at the level of the natural waist or the narrowest part of the torso from the anterior side. Measurements were taken by trained technicians with participants wearing nonrestrictive undergarments. The use of standard subjective measurements minimized the potential measurement error.

MetS groups used in the current study: At baseline, women with fewer than three MetS components were categorized into the "no MetS" group. The rest of the women with at least three MetS components irrespective of their HDL status were classified as having MetS and then categorized into two groups based on their HDL status: 1) MetS whose HDL-C $\geq$ 50 mg/dL (MetS hiHDL), and 2) MetS whose HDL-C $<$ 50 mg/dL (MetS loHDL). As such, the analysis used these three MetS groups as the primary exposure variable. The main analysis assessed the prospective association of baseline MetS groups with future cIMT at V12 and incident diabetes by V16.

2.5. Study covariates

Race/ethnicity (White, Black, Hispanics, Chinese and Japanese) was self-reported at the SWAN baseline visit. Age, menopause status, smoking status, and alcohol consumption were collected at each SWAN visit. Age was calculated as the difference between the visit date and birth date. Menopause status was determined based on participants' reported menstrual bleeding patterns and categorized as follows: premenopausal (no change in menstrual bleeding and cycles), early perimenopausal (at least one menstrual bleeding in the last three months and some changes in the intervals of the menstrual cycles), late perimenopausal (at least one menstrual cycle within the past 12 months but no bleeding within the past 3 months), postmenopausal (no menstrual cycle within the past 12 months due to natural or surgical menopause [bilateral oophorectomy]) or unknown status due to hormone therapy use or hysterectomy. Smoking status was self-reported and categorized as current smokers versus past/never smokers. Alcohol consumption status was also self-reported and categorized as having more than 1 drink per month versus having less than 1 drink per month. Physical activity scores were collected using the Kaiser Physical Activity Survey

[22], which is validated self-administered questionnaire. Hormone therapy use was defined as use of hormone therapy use since last visit.

2.6. Statistical analysis

After testing for normality by checking the distributions of variables visually and performing the Shapiro-Wilk test, skewed continuous variables were log-transformed and summarized as either mean (SD) or median (Q1, Q3), while categorical variables were summarized as frequency (percentage). Normality assumptions, outliers and influential points were checked before performing regression analysis. Unadjusted and multivariable adjusted linear regression analysis was used to assess the associations between baseline MetS groups (no MetS (reference), MetS hiHDL, MetS loHDL) and cIMT from SWAN visit 12 or 13 adjusting for baseline age, study site, race/ethnicity, menopausal status, smoking status, and alcohol consumption in the multivariable regression models. We additionally adjusted models for levels of systolic blood pressure, fasting glucose, waist circumference, and triglycerides at baseline to assess whether levels of components of MeS other than HDL-C explain the tested association. For the linear regression models, point estimates (β) represent mean difference in cIMT of each of the MetS group compared to the reference group (No MetS).

Discrete-time survival analysis [23] was used to assess the associations between MetS groups and incident diabetes to deal with the yearly collected incident diabetes data. Descriptive survival curves generated for the three baseline MetS groups using the life table approach to present time-to-diabetes with right censoring. Univariate discrete time survival analysis was used to assess the unadjusted association. The multivariable analysis between baseline MetS groups and incident diabetes were adjusted for study site, race/ethnicity, and time-varying age, menopausal status, smoking status, and alcohol consumption, with additional adjustment for time-varying systolic blood pressure, waist circumference, and triglycerides in the final model. For the discrete-time survival analysis, hazard ratios (HR) and the corresponding 95 % confidence interval represent differences in hazard risk for developing incident diabetes in each of the MetS group compared to no MetS group. Missing data of time varying covariates were imputed using multiple imputation. Bonferroni correction was used for multiple testing.

The interaction between race/ethnicity and MetS groups was tested for both outcomes. A sensitivity analysis was conducted for MetS groups at visit 12 and cIMT at visit 12 or 13.

All analyses were conducted using SAS 9.4 (SAS Institute, Cary, CA) with a significance level set at $p < 0.05$. RStudio (version 4.1) was used for generating visualizations.

3. Results

3.1. Baseline characteristics

Characteristics for 2773 SWAN participants included in this analysis stratified by MetS group are summarized in Table 1. At the baseline SWAN visit, 86.3 % of the women ($n = 2383$) had no MetS, 4.1 % of the women ($n = 117$) belonged to the MetS hiHDL group, and 9.6 % of the women ($n = 273$) belonged to the MetS loHDL group. A total of 286 participants developed diabetes during the follow-up. Women with MetS and high HDL-C were more likely to be Black (59.0 %) and premenopausal (53.9 %). Compared to women with no MetS, women with MetS, regardless of their HDL-C levels, were older and had significantly higher levels blood pressure, waist circumference, LDL-C, ApoB, ApoA1, total cholesterol, blood glucose and triglycerides, Table 1. Compared to women with MetS and low HDL-C, women with MetS and high HDL-C were significantly older, had higher levels of systolic blood pressure (SBP), diastolic blood pressure (DBP), Apolipoprotein AI (ApoA1), and cIMT. Besides these characteristics, the two groups had similar levels of clinical measures. The mean time between baseline MetS group identification and cIMT measurements is 13.8 years.

3.2. Associations between baseline MetS status and cIMT

As shown in Table 2 and Fig. 3, compared to women with no MetS at baseline, women in any of the two MetS groups had significantly higher levels of cIMT in the unadjusted models, regardless of their HDL-C levels. In models adjusting for study site, race/ethnicity, baseline age, menopausal status, smoking status, alcohol consumption, and physical activity, the associations were attenuated but remained significant. The associations were not significant adjusting for other components of the metabolic syndrome, including systolic blood pressure, log-transformed glucose level, waist circumference, log-transformed TG levels. cIMT level did not differ between MetS loHDL vs. MetS hiHDL groups. Similar results were observed when MetS was defined at the same time as the cIMT measurement, as shown in Table S1. In all models, race did not modify the associations between MetS status and cIMT.

Table 1
Baseline characteristics of SWAN participants by MetS status ($n = 2773$).

Variables	No MetS ($n = 2383$)	MetS hiHDL ($n = 117$)	MetS loHDL ($n = 273$)
Age	45.8 (2.7)	47.0 (2.7)[a,b]	46.1 (2.8)
BMI	26.3 (6.1)	35.7 (7.5)[a]	36.2 (6.9)[a]
SBP	114.6 (15.2)	137.5 (19.1)[a,b]	130.5 (18.4)[a]
DBP	73.8 (9.9)	84.5 (10.4)[a,b]	81.5 (11.0)[a]
Waist circumference	81.6 (13.2)	103.3 (14.5)[a]	106.6 (14.0)[a]
ApoA1	153.2 (25.0)	162.4 (20.8)[a,b]	133.3 (17.2)[a]
ApoB	106.1 (26.3)	126.6 (30.9)[a,b]	135.2 (34.4)[a]
LDL-C	113.5 (29.8)	126.5 (34.1)[a]	126.2 (34.3)[a]
HDL-C	59.6 (13.8)	57.8 (8.1)[b]	39.6 (6.0)[a]
Total cholesterol	191.3 (32.7)	214.7 (36.7)[a]	209.2 (41.6)[a]
Fasting glucose	87.0 (14.9)	123.5 (56.1)[a,b]	131.9 (60.5)[a]
Triglycerides	81 (63, 107)	151 (94, 193)[a,b]	197.5 (155, 251)[a]
cIMT at V12/13[c]	0.78 (0.12)	0.85 (0.15)[a]	0.83 (0.13)[a]
Physical activity scores	7.82 (1.77)	6.88 (1.71)[a]	6.99 (1.67)[a]
Race, N(%)			
Black	610 (25.6)	69 (59.0)	91 (33.6)
White	1160 (48.7)	27 (23.1)	124 (45.4)
Chinese	199 (8.4)	5 (4.3)	10 (3.7)
Hispanic	174 (7.3)	9 (7.7)	35 (12.8)
Japanese	239 (10.0)	7 (6.0)	13 (4.8)
Menopausal status, N (%)			
Pre-menopause	1313 (55.3)	63 (53.9)	129 (47.3)
Early peri-menopause	1050 (44.7)	54 (46.2)	144 (52.8)
Unknown	2 (0.1)	0 (0)	0 (0)
Smoking status, N (%)			
Never smoker	1406 (59.1)	67 (57.3)	127 (46.7)
Past smoker/Current smokers	974 (40.9)	50 (42.7)	146 (53.3)
Alcohol intake, N (%)			
Less than one drink per month	1096 (46.1)	66 (56.9)	178 (65.0)
More than one drink per month	1280 (53.9)	50 (43.1)	96 (35.0)

apoA1: apolipoprotein A1; ApoB: apolipoprotein B; BMI: body mass index; cIMT: carotid intimal-medial wall thickness; DBP: diastolic blood pressure; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein; MetS: metabolic syndrome; SBP: systolic blood pressure.

[a] Significantly different from No MetS group.

[b] Significantly different from MetS loHDL group.

[c] N=1317.

3.3. Associations between baseline MetS and incident diabetes

In the unadjusted models, women in any of the two MetS groups had significantly higher hazard of developing diabetes compared to women with no MetS, regardless of HDL-C levels. The associations attenuated but remained significant after adjusting for time-varying age, menopausal status, smoking status, alcohol consumption, physical activity and hormone therapy use. Further adjustment of time-varying systolic blood pressure, waist circumference, log-transformed TG levels did not explain the differences in hazards between baseline MetS status and incident diabetes. Moreover, in all models, women with MetS and low HDL-C had significantly higher hazard of developing diabetes compared women with MetS and high HDL-C, Table 2 and Fig. 3. Race modified the associations between MetS status and incident diabetes in the unadjusted models only.

The survival curves stratified by baseline MetS showed highest probabilities of incident diabetes for the MetS loHDL group and the lowest probabilities for the no MetS group. Women with MetS and high HDL-C were at elevated hazard of developing diabetes compared to women with no MetS, but their hazard was lower compared to women with MetS and low HDL-C, Fig. 2.

4. Discussion

Our study investigated the contribution of HDL-C, as a criterion of MetS, to the MetS associated risk with surrogate measure of subclinical atherosclerosis and incident diabetes among midlife women transitioning through menopause. Our analysis showed that levels of future cIMT did not differ between the MetS loHDL and MetS hiHDL groups, suggesting a lack of contribution of HDL-C classification to cIMT, a surrogate marker of subclinical vascular health, in relation to MetS status. On the other hand, the hazards of incident diabetes were significantly greater in the MetS loHDL group than the MetS hiHDL independent of levels of other MetS components. This suggests that HDL-C status classification contributes significantly to the risk of incident diabetes but not higher cIMT beyond other MetS components in midlife women. Our findings underscored differential contributions of HDL-C to MetS based on outcome of interest. The contribution of low HDL-C seems to be critical to the risk of incident diabetes but not to the higher level of cIMT in midlife women with MetS.

There is a lack of understanding of the contribution of HDL-C to cardiovascular diseases in midlife women. Current studies tend to either generalize findings from boarder age groups or lack a good representation of women participants. One previous systematic review involving over 3459 middle-aged participants (mean age 57.8 years, 29.3 % female) from 7 clinical trials found that HDL-C levels alone or HDL-C levels in combination with metabolic syndrome were not significantly associated with the odds of plaque progression, which is another common surrogate measure of subclinical atherosclerosis [24]. Our analysis results for cIMT are consistent with this finding. In contrast, a study of 2650 cardiovascular disease-free men and women aged 35–74 years found that HDL-C levels and systolic blood pressure were the only two contributing MetS criteria predicting CHD and CVD events [25]. However, it is important to note that the age range of the participants was broader than in our sample, and the results were not specific to women.

Our results suggested different contributions of HDL-C to levels of surrogate measure of subclinical atherosclerosis and diabetes development, which may be caused by the different mechanistic pathways of HDL-C within the two different outcomes. Recent findings have shown that high levels of HDL-C in midlife and older women is not always cardio-protective. Previous studies have suggested the adverse changes in the atheroprotective function of HDL-C under chronic inflammation, including atherosclerosis [26]. A research work from the Multi-Ethnic Study of Atherosclerosis (MESA) showed that higher HDL-C was not associated with lower cIMT but with a greater risk of having the presence of carotid plaque [3]. Findings from genetic studies also found that a variant of the hepatic HDL scavenger receptor B1, encoded in the SCARB1 gene, raised HDL-C levels but also raised coronary heart disease risks [27,28], suggesting again that the absolute level of HDL-C may be unreliable. These findings have suggested that HDL-C, as a crude measure of total HDL contents, may not reflect true CVD risk.

On the other hand, low HDL-C is one of the well-recognized risk

Table 2
Associations between baseline MetS and future cIMT or incident diabetes.

	cIMT (mm) (n = 1317)		Incident diabetes (n = 2640)	
Models[a]	β (SE)	P-value	HR (95 % CI)	P-value
Unadjusted				
MetS hiHDL	0.06 (0.02)	0.0003	5.92 (3.92, 8.95)[b]	0.005
MetS loHDL	0.05 (0.01)	<0.0001	10.9 (8.92, 14.2)	<0.0001
Adjusted Model 1				
MetS hiHDL	0.04 (0.02)	0.02	4.44 (2.91, 6.78)[b]	<0.0001
MetS loHDL	0.03 (0.01)	0.001	9.78 (7.44, 12.9)	<0.0001
Adjusted Model 2				
MetS hiHDL	−0.01 (0.02)	0.527	2.47 (1.58, 3.84)[b]	<0.0001
MetS loHDL	−0.02 (0.01)	0.150	5.26 (3.88, 7.14)	<0.0001

Adjusted Model 1: Adjusting for study site, race/ethnicity, baseline age, menopausal status, smoking status, alcohol consumption, physical activity for cIMT; adjusting for study site, race/ethnicity, time-varying age, menopausal status, smoking status, alcohol consumption, physical activity and hormone therapy use for diabetes.

Adjusted Model 2: Model 1 + baseline systolic blood pressure, log-transformed glucose levels, waist circumference, log-transformed TG levels for cIMT; time-varying systolic blood pressure, waist circumference, log-transformed TG levels for diabetes.

[a] No MetS as the reference group.

[b] Significant differences between MetS high and low groups.

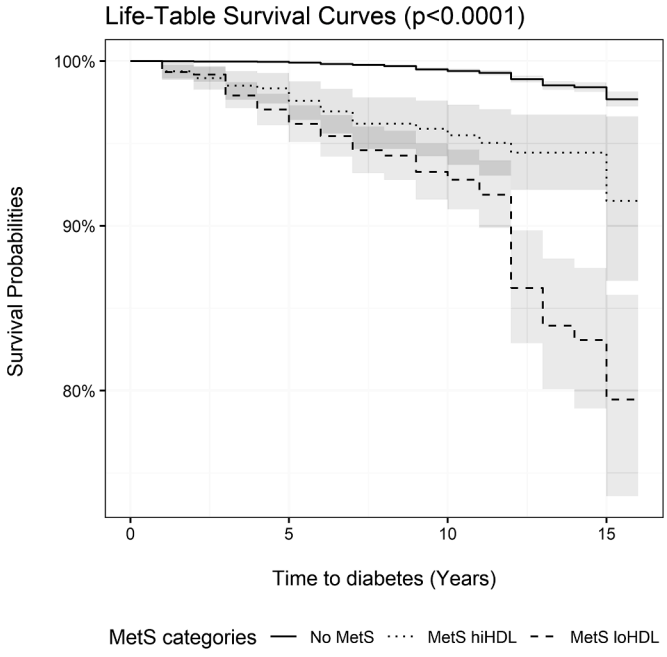

Fig. 2. Unadjusted Life-Table survival curves of incident diabetes stratified by MetS categories.

The unadjusted survival curves were generated using the Life-Table method. The x-axis represented the time to diabetes in years (0–16), and the y-axis represented the survival probabilities. The red line was the survival curve for participants with no MetS, the green line was the survival curve for participants from the MetS hiHDL category, and the black line was the survival curve for participants from the MetS loHDL category. The 95 % confidence intervals were the corresponding area surrounding each survival curves. P-value is from log-rank test.

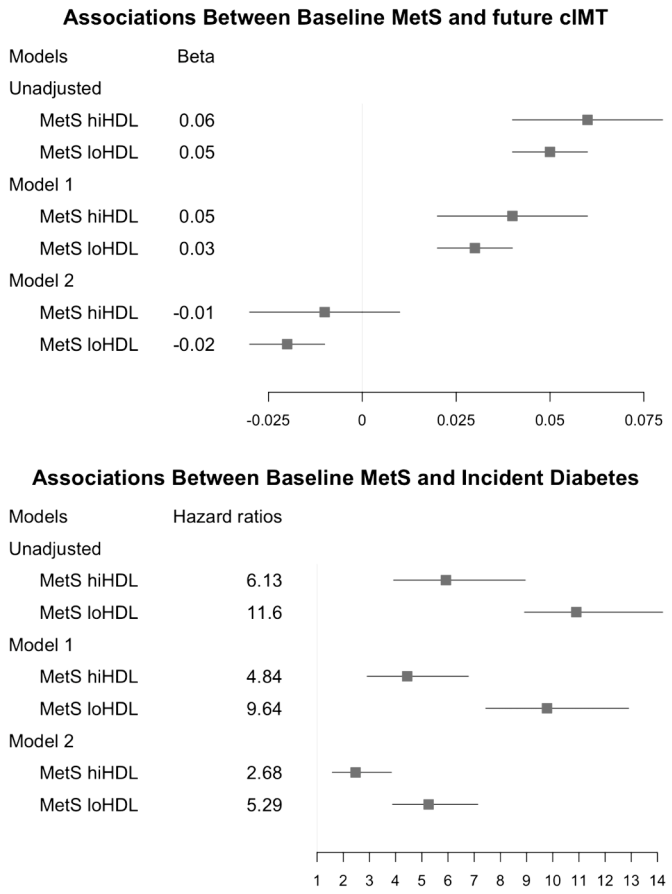

Fig. 3. Forest plots of the associations between baseline MetS and cIMT/incident diabetes.
Each square point indicated the point estimate, and the horizontal line around each square point represented the corresponding 95 % confidence interval for each point estimate.
Model 1: Adjusting for study site, race/ethnicity, baseline age, menopausal status, smoking status, alcohol consumption, physical activity for cIMT; adjusting for study site, race/ethnicity, time-varying age, menopausal status, smoking status, alcohol consumption, physical activity and hormone therapy use for diabetes.
Model 2: Model 1 + baseline systolic blood pressure, log-transformed glucose level, waist circumference, log-transformed TG levels for cIMT; time-varying systolic blood pressure, waist circumference, log-transformed TG levels for diabetes.

factors of diabetic dyslipidemia [29]. Recent studies found that mechanistically, lower HDL-C levels can lead to beta-cell dysfunction, thereby inhibiting the secretion of insulin, and consequently related to diabetes [30,31]. Although the precise mechanism between HDL-C and diabetes is unknown, rising evidence has suggested a direct impact of HDL-C on insulin secretion and insulin sensitivity [32]. Studies in humans have found genetic variations in the ATP-binding cassette subfamily A member 1 (ABCA1), which is a major cellular cholesterol transporter, can lead to impairment in cholesterol efflux capacity that relates to both lower HDL-C levels and higher risks of developing diabetes [33]. All the findings indicate the potential role of HDL-C in glucose metabolism [34].

Our findings suggest that among women diagnosed with MetS, meeting the diagnostic criteria is related to higher cIMT regardless of their HDL-C levels. Previous meta-analysis of 12 randomized controlled trials targeting HDL-C raising drugs also showed no significant difference in the risk of CVD between the treatment and control groups [35]. Our findings, with the growth body of evidence that documented the adverse functional changes of HDL-C, have suggested the importance of including other functional measures of HDL into the diagnosis of MetS. On the other hand, experiential evidence has shown that HDL-C may play a beneficial role in increasing the pancreatic beta cell function, thus enhance the plasma glucose metabolism [36].

Currently, pharmacologic treatment to prevent diabetes is limited. The cholesteryl ester transfer protein (CETP) inhibitors can be used to improve blood lipid levels, with a potential of lowering risk of diabetes [37]. A recent meta-analysis found that CETP inhibitors were associated with a 16 % reduction of new onset of diabetes, and also with improvements in glycemic measures, such as fasting glucose and insulin levels [37]. Although current knowledge of the effect of HDL-C raising drugs on diabetes risk is limited, lifestyle changes are shown to be effective in raising HDL-C and aid diabetes prevention.

The study has several major strengths, including its prospective design and large sample size. The SWAN study collected incident diabetes data over a 16-year period, allowing for a better understanding of the long-term impact of midlife MetS status on diabetes. Additionally, the study gathered a comprehensive set of potential confounders, including demographic, lifestyle, and clinical measures, ensuring comprehensive adjustment in the analysis. The analysis also accounted for time-varying covariates, capturing changes in the impact of confounders over time. The use of multiple imputation to handle missing data improved the accuracy of coefficient estimates and maintained an adequate sample size for the diabetes analysis.

However, the study also has several limitations. Firstly, the number of participants with MetS and high HDL-C was relatively small, which may limit the generalizability of the findings. Secondly, the study did not account for changes in MetS status during the follow-up period. Nevertheless, sensitivity analysis conducted on MetS status at later SWAN visits and cIMT showed consistent results with the main analysis, suggesting a stable association between MetS status and cIMT over time. Thirdly, the relatively small number of participants with incident diabetes in some visits resulted in wider 95 % confidence intervals for hazard ratio estimates. Moreover, although this analysis accounted for many confounders, there could be unmeasured confounders that can lead to bias. Finally, due to the yearly collection of diabetes data, the analysis was performed using discrete-time survival models.

Interestingly, more studies have focused on the predictability of HDL subclasses in patients with MetS on their CVD risks, in addition to HDL-C [38,39]. The SWAN HDL ancillary study provides unique data on HDL subclasses, lipid content, and HDL particle functions in midlife women going through menopause [40]. As the next step, it is necessary to assess how novel HDL metrics are associated with MetS and surrogate measure of subclinical atherosclerosis using the SWAN HDL data. This assessment will contribute to the current understanding of the utility of HDL subclasses. Understanding the association between the various components of MetS and the risk of developing diabetes and CVD in midlife women is clinically important due to the high prevalence of MetS in this population [8].

The findings have significant implications for understanding the associations between MetS and cardiometabolic diseases. The concept of MetS emerged largely due to the recognition of a clustering of risk factors for coronary heart disease and diabetes among patients with abdominal obesity. However, it remains questionable whether MetS represents a pathological condition or just an association of risk factors. These results further support the concept that a clinical diagnosis of MetS highlights the patient's atherogenic risk, and that treating components other than HDL-C may be helpful to lower CVD risks. Previous research has also underscored the importance of treating the components of MetS, particularly high triglycerides and large waist circumference, which could contribute to reducing the risk of CVD [24]. Although our findings indicate that the risk of having high levels of cIMT did not differ between women with MetS with high vs. low HDL-C levels, given that low HDL-C is still a strong risk factor for diabetes, both therapeutic and lifestyle changes that increase HDL-C levels could still confer long-term benefits for midlife women against cardiometabolic

disease.

5. Conclusion

In conclusion, midlife women with MetS face an increased risk of developing incident diabetes and exhibit higher levels of subclinical measures of atherosclerosis. While cIMT can be attributed to MetS criteria other than HDL-C, the same explanation does not hold true for incident diabetes. These findings suggest that HDL-C levels are differentially related to various cardiovascular outcomes among midlife women transitioning through menopause. Our findings also highlight the necessity of interventions with favorable cardiometabolic impact, such as exercise, that raise HDL-C particularly among women with MetS. Consequently, further studies are needed to explore the predictive role of HDL-C in cardiovascular risks specifically in midlife women.

CRediT authorship contribution statement

Ziyuan Wang: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Emma Barinas-Mitchell:** Writing – review & editing, Data curation. **Maria M. Brooks:** Writing – review & editing, Investigation. **Sybil L. Crawford:** Writing – review & editing. **Aleda M. Leis:** Writing – review & editing. **Carol A. Derby:** Conceptualization, Methodology, Writing – review & editing, Project administration, Funding acquisition. **Rebecca C. Thurston:** Writing – review & editing, Investigation. **Monique M. Hedderson:** Writing – review & editing. **Imke Janssen:** Writing – review & editing. **Elizabeth A. Jackson:** Writing – review & editing. **Daniel S. McConnell:** Resources, Methodology, Writing – review & editing, Project administration, Funding acquisition. **Samar R. El Khoudary:** Writing – review & editing, Supervision, Investigation, Conceptualization.

Declaration of competing interest

We wish to draw the attention of the Editor to the following facts which may be considered as potential conflicts of interest and to significant financial contributions to this work. Dr. Rebecca Thurston is a consultant and advisor for Astellas Pharma, consultant and received travel support from Bayer, and on the medical advisory board for Hello Therapeutics. All other coauthors have nothing to disclose.

Acknowledgements

Clinical Centers: University of Michigan, Ann Arbor – Carrie Karvonen-Gutierrez, PI 2021 – present, Siobán Harlow, PI 2011 – 2021, MaryFran Sowers, PI 1994–2011; Massachusetts General Hospital, Boston, MA – Sherri-Ann Burnett-Bowie, PI 2020 – Present; Joel Finkelstein, PI 1999 – 2020; Robert Neer, PI 1994 – 1999; Rush University, Rush University Medical Center, Chicago, IL – Imke Janssen, PI 2020 – Present; Howard Kravitz, PI 2009 – 2020; Lynda Powell, PI 1994 – 2009; University of California, Davis/Kaiser – Elaine Waetjen and Monique Hedderson, PIs 2020 – Present; Ellen Gold, PI 1994 - 2020; University of California, Los Angeles – Arun Karlamangla, PI 2020 – Present; Gail Greendale, PI 1994 - 2020; Albert Einstein College of Medicine, Bronx, NY – Carol Derby, PI 2011 – present, Rachel Wildman, PI 2010 – 2011; Nanette Santoro, PI 2004 – 2010; University of Medicine and Dentistry – New Jersey Medical School, Newark – Gerson Weiss, PI 1994 – 2004; and the University of Pittsburgh, Pittsburgh, PA – Rebecca Thurston, PI 2020 – Present; Karen Matthews, PI 1994 - 2020.

NIH Program Office: National Institute on Aging, Bethesda, MD – Rosaly Correa-de-Araujo 2020 - present; Chhanda Dutta 2016- present; Winifred Rossi 2012–2016; Sherry Sherman 1994 – 2012; Marcia Ory 1994 – 2001; National Institute of Nursing Research, Bethesda, MD – Program Officers.

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Steering Committee: Susan Johnson, Current Chair; Chris Gallagher, Former Chair.

We thank the study staff at each site and all the women who participated in SWAN.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2024.100687.

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