



Fat distribution and plasma lipid-lipoprotein concentrations in pre- and postmenopausal women

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OBJECTIVE: In the postmenopausal years, women develop a central pattern of fat distribution and an increased risk of developing cardiovascular disease (CVD). The possibility that these events are related has not been extensively investigated. The object of the present study was to test the hypotheses that, 1) menopause-related differences in lipids are associated with greater estimated intra-abdominal adiposity, and 2) the relationship between individual adipose depots and plasma lipids differs with menopausal status.

DESIGN: Cross-sectional.

SUBJECTS: 141 healthy pre- and postmenopausal women aged 35–65 y.

MEASUREMENTS: Total body fat by hydrodensitometry was used as an index of whole-body adiposity, the sum of five central skinfold measurements as an index of subcutaneous upper-body adiposity, and estimated intra-abdominal adipose tissue (IAF) as an index of visceral adiposity. Fasting plasma concentrations of total cholesterol (total-C), high- and low-density-lipoprotein cholesterol (HDL-C, LDL-C), and triglycerides were used as indices of CVD risk.

RESULTS: Postmenopausal women had greater total body fat ($P < 0.001$), summed central skinfolds ($P < 0.01$), estimated IAF ($P < 0.001$), higher plasma concentrations of total-C ($P < 0.001$), LDL-C ($P < 0.001$) and triglycerides ($P < 0.001$), than premenopausal women. The relationship between central skinfolds and LDL-C differed with menopausal status, being significant in pre- but not postmenopausal women. Adjustment for estimated IAF with analysis of covariance decreased menopause-related differences in levels of total-C, LDL-C and triglycerides by approx 40–70%.

CONCLUSION: These observations suggest that, 1) menopause-related changes in IAF may adversely affect the plasma lipid profile, and 2) menopausal status affects the relationship between central subcutaneous fat and LDL-C. Studies with measured IAF are needed to confirm present results.

Keywords: fat distribution; menopause; lipids

Introduction

The incidence of cardiovascular disease (CVD) increases following menopause.¹ This may be due, in part, to changes in plasma lipid-lipoprotein levels that occur following the menopausal transition. Elevated total cholesterol, LDL-cholesterol and triglycerides, are more common in post- than premenopausal women.^{2–5}

Deposition of intra-abdominal fat (IAF) may explain some of the changes in plasma lipid-lipoprotein levels following menopause. Prior to menopause, adipose tissue is deposited preferentially in the gluteo-femoral (gynoid) area. However following menopause, fat is increasingly deposited in the central (upper-body) region.^{5–7} Intra-abdominal adipose tissue is associated with the constellation of metabolic disturbances, termed 'syndrome X',⁸ which includes insulin resistance, hyperinsulinaemia, low

HDL-cholesterol, high apolipoprotein B and high triglycerides.⁹ Although central adiposity is associated with CVD incidence in women,¹⁰ the possibility that changes in fat distribution contribute to the increase in CVD risk associated with menopause has not been widely investigated.

The present study was undertaken to examine the relationship between fat distribution and concentrations of circulating lipids in pre- and postmenopausal women. Using cross-sectional data from 141 women aged 35–65 y and an estimation of IAF, we tested the hypotheses that, 1) menopause-related differences in lipids are associated with greater intra-abdominal adiposity, and that, 2) the relationship between individual adipose depots and plasma lipids differs with menopausal status.

Methods

Subjects

Healthy Caucasian (white) women aged 35–65 y ($n = 141$) recruited from the Burlington, Vermont,

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and the Chittenden County metropolitan area, participated in the study. Volunteers were recruited by advertisements in newspapers, radio announcements and other means. Subjects had no symptoms of heart disease (resting blood pressure < 140/90 mmHg, normal resting electrocardiogram); were taking no medications that could affect lipid metabolism; had no medical history of diabetes; and were weight-stable (2 kg) by medical history within the past year. Subjects were considered postmenopausal if they reported an absence of menstrual cycles for at least 12 months. None of the postmenopausal women was taking, or had ever taken, hormone replacement therapy. Women who had undergone surgical menopause (oophorectomy) were excluded from the study. For all tests, premenopausal women were examined during the follicular phase of the menstrual cycle. All blood was drawn after a 12-h overnight fast. The average age of menopause in this population was 50 ± 2 y, similar to the median age of 51.5 y reported elsewhere.¹¹ The nature, purpose and possible risks of the study, were carefully explained to each subject before she gave consent to participate. The experimental protocol was approved by the Committee on Human Research for the Medical Sciences of the University of Vermont.

Fat distribution

Fat mass was determined by hydrodensitometry (using the equation of Siri¹²), with simultaneous measurement of residual lung volume by helium dilution. The coefficient of variation of this measurement in our laboratory is 4.2%. Skinfold measurements were taken at five central sites (abdomen, axillary, chest, subscapular and suprailiac) and four peripheral sites (thigh, calf, biceps and triceps). The mean of three consecutive measurements was used. Waist circumference was measured at the minimal point between the xiphoid process and superior iliac crest (approximately at the umbilicus) with a flexible tape. All measurements were performed by the same investigator.

IAF was estimated using a prediction equation based on age, waist circumference and suprailiac skinfold:¹³ $IAF = [(waist\ circumference \times 2.57) + (age \times 0.92) + (suprailiac\ skinfold \times 0.69) - 188.61]$; model $R^2 = 0.75$. This equation was developed in 153 women ranging in age from 17–76 y, comprising approximately 40% postmenopausal women. To develop the equation, anthropometric variables were first subject to factor analysis with orthogonal rotation. Correlations were then computed between variables with the largest factor loadings, as well as derived variables known from previous studies to predict IAF. The predictor variables with the lowest correlations among themselves and the highest correlations with IAF, were subject to stepwise regression analysis. A minimal tolerance criterion of 0.3 was used to eliminate potential multicollinearity problems. The resultant equation was successfully cross-validated in an independent sample of 51

women ($R^2 = 0.79$), and in pre- and postmenopausal subpopulations of this validation sample (approximately 26% and 33% body fat, and 50 and 100 cm² IAF for pre- and postmenopausal subjects, respectively). The population used for the development of the prediction equation was similar with respect to range in adiposity to the present subject population (9–48% fat in the development population and 9–55% fat in the present population) and was predominantly Caucasian.

Plasma lipid analyses

Total cholesterol (total-C) and triglycerides were determined by enzymatic processes;^{14,15} HDL-cholesterol (HDL-C) after precipitation of low-density-lipoprotein cholesterol (LDL-C) and very-low-density lipoprotein cholesterol (VLDL-C) with dextran sulfate;¹⁶ and LDL-C with the method of Freidewald *et al*¹⁷ ($LDL-C = total\ cholesterol - (HDL-C + triglycerides/5)$); all subjects had triglyceride levels below 4.5 mmol/L). Coefficients of variation for cholesterol and triglyceride measurements were 5% and 3%, respectively.

Statistical analyses

For statistical analyses, the following parameters were used: body fat determined by hydrodensitometry as an index of whole-body adiposity, the sum of the five central skinfold measurements as an index of subcutaneous upper-body adiposity, and IAF, estimated with a prediction equation, as an index of visceral adiposity. Preliminary analyses conducted with summed peripheral skinfold measurements indicated that this parameter was not independently related to the dependent variables and its inclusion in analyses did not affect results shown herein; thus, these data are not presented. Since lipid values were not normally distributed, all were log transformed prior to analyses (transformed values were normally distributed). With the exception of Fisher's Z test, analyses were conducted with SAS Institute, Inc. software, version 6.10 for Windows. Fisher's Z test was conducted with 'Pow Cor' (D. Allison and B.S. Gorman, © 1993, Reference: Allison DB, Gorman BS. POWCOR: A power analysis and sample size program for testing differences between dependent and independent correlations. *Educational & Psychological Measurement*, S3: 133–137). Analysis of variance (ANOVA) was used to determine if menopausal status affected plasma lipids. Pearson correlation coefficients between anthropometric parameters, age and risk factors were generated for pre- and postmenopausal women separately. Fisher's Z test was used to determine whether the relationships between central skinfolds and lipids (total-C, LDL-C and triglycerides), and between estimated IAF and lipids (total-C, LDL-C and triglycerides) differed with menopausal status. Multiple linear regression was used (groups combined) to determine if age had an independent effect on lipids-lipoproteins, after controlling for menopausal status and adiposity (three analyses were

conducted, using total fat mass, central skinfold and estimated IAF, in turn). Stepwise multiple linear regression was conducted within the pre- and postmenopausal groups, to identify factors explaining variation in those lipid-lipoprotein variables that differed with menopausal status. Significance was set at $P < 0.05$ for variable entry and $P > 0.05$ for variable removal. Independent variables were total fat mass, summed central skinfolds and estimated IAF. Analysis of covariance (ANCOVA) was used to examine relationships between meno-pausal status and lipids-lipoproteins, after controlling for covariates identified in stepwise multiple linear regression.

Results

Subject characteristics

Descriptive statistics are given in Table 1. Analysis of variance indicated that postmenopausal women were older, weighed more, had greater body fat (percent and absolute), central skinfolds, estimated IAF ($P < 0.001$, 0.01 and 0.001, respectively), waist circumference, total-C, LDL-C and triglycerides ($P < 0.001$ for all) than premenopausal women. HDL-C did not differ with menopausal status.

Menopause, fat distribution and plasma lipids

Pearson correlation analysis indicated that total-C was associated with total fat, central skinfolds and estimated IAF in both groups of women (r values ranging from 0.29–0.51). LDL-C was related to central skinfolds in pre-, but not postmenopausal women (Figure 1); was related to estimated IAF in both groups ($r = 0.48$ and 0.23 in pre- and postmenopausal groups, respectively); and was related to total fat in pre- ($r = 0.46$) but not postmenopausal women. HDL-C was not related to any measure of adiposity in either group. Triglycerides were related only to indices of central adiposity (central skinfolds and estimated IAF) in both groups of women (r values ranging

Table 1 Descriptive statistics

	Premenopausal (<i>n</i> = 63)	Postmenopausal (<i>n</i> = 78)
Age (y)	42 ± 5	59 ± 5**
Body mass (kg)	61 ± 9	64 ± 9
Percent fat	26 ± 8	35 ± 6**
Body mass index	23 ± 3	24 ± 3
Fat mass (kg)	16 ± 7	22 ± 6**
Central skinfolds (mm)	80 ± 35	97 ± 29*
Estimated IAF (cm ²)	51 ± 27	82 ± 26**
Waist circumference (cm)	71 ± 8	76 ± 8**
Total cholesterol (mmol/L)	4.7 ± 0.9	5.5 ± 0.9**
HDL-C (mmol/L)	1.4 ± 0.3	1.5 ± 0.4
LDL-C (mmol/L)	2.7 ± 0.8	3.4 ± 0.8**
Triglycerides (mmol/L)	1.0 ± 0.4	1.2 ± 0.5**

Values are mean ± s.d. (geometric mean ± s.d. for lipid-lipoprotein values).

* $P < 0.01$ ** $P < 0.001$.

HDL-C = high-density lipoprotein cholesterol.

LDL-C = low-density lipoprotein cholesterol.

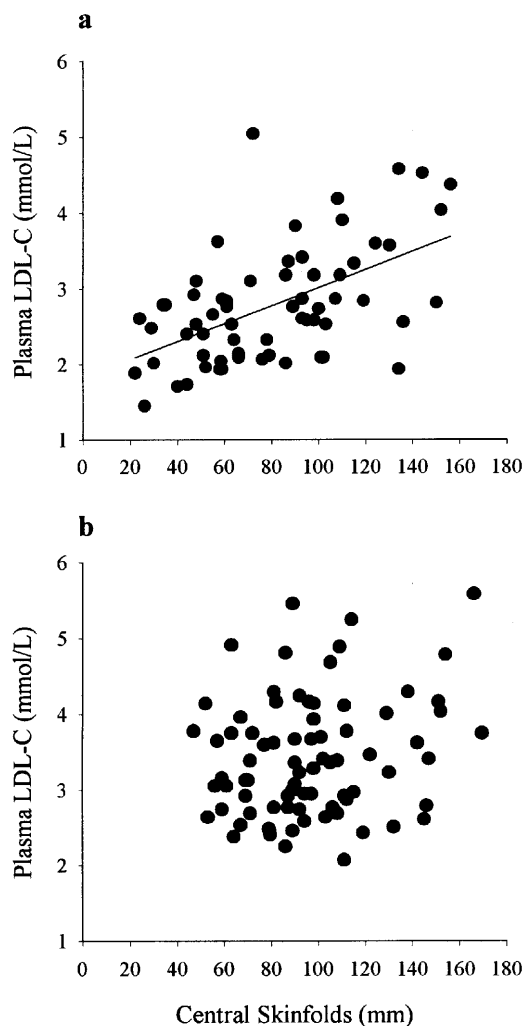


Figure 1 Relationship between low-density lipoprotein cholesterol (LDL-C) and summed central skinfolds in pre- (a, $R^2 = 0.29$, $P < 0.05$) and postmenopausal (b, non-significant) women.

from 0.28–0.44). Fisher's; Z test indicated that the correlation between central skinfolds and LDL-C differed with menopausal status (two-tailed $P < 0.05$); no other comparisons were significant. Triglyceride concentration was correlated with HDL-C concentration in both groups (premenopausal women: $r = -0.41$, $P < 0.001$; postmenopausal women: $r = -0.26$, $P < 0.05$).

In stepwise multiple linear regression of data from premenopausal women, summed central skinfolds was the only variable to enter the model for total- and LDL-C (Table 2, a). For triglycerides, central skinfolds entered the model first, and an additional 6% of the variance was explained by total body fat. Among postmenopausal women, estimated IAF was the only variable to enter the models for total- and LDL-C and triglycerides (Table 2, b). The relationship between estimated IAF and triglyceride concentration in pre- and postmenopausal women is depicted in Figure 2, a and b, respectively.

Adjustment for estimated IAF with analysis of covariance, decreased menopause-related differences in levels of total-C, LDL-C and triglycerides by 44%, 46% and 73%, respectively (Table 3). The analysis

Table 2 Stepwise multiple linear regression coefficients for central skinfolds (a, premenopausal group) and estimated IAF (b, postmenopausal group) with the dependent variables indicated

Dependent variable	P	β	Model R ²
a) premenopausal women			
Log total-C	$P < 0.001$	0.001	0.26
Log LDL-C	$P < 0.001$	0.002	0.29
Log triglycerides*	$P < 0.01$	0.004	0.12
b) postmenopausal women			
Log total-C	$P < 0.01$	0.001	0.12
Log LDL-C	$P < 0.05$	0.001	0.05
Log triglycerides	$P < 0.001$	0.003	0.20

*Total fat mass entered the model after central skinfolds and explained an additional 6% of the variance ($\beta = -0.013$; $P < 0.05$). total C = total cholesterol; LDL-C = low-density lipoprotein cholesterol.

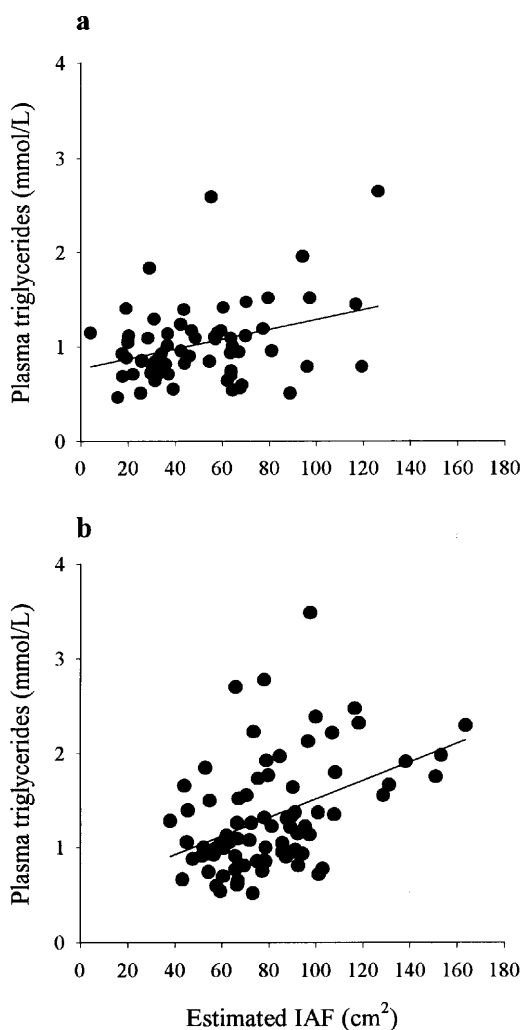


Figure 2 Relationship between triglycerides and estimated intra-abdominal adipose tissue (IAF) in pre- (a, $R^2 = 0.08$, $P < 0.05$) and postmenopausal (b, $R^2 = 0.19$, $P < 0.01$) women.

indicated that the slope of the relationship between central skinfolds and LDL-C differed in pre- vs postmenopausal women (Figure 1).

Age

Age was not correlated with triglycerides in either group, and was correlated with total- and LDL-C in

postmenopausal women only ($r = 0.27$ and 0.24 , respectively; $P < 0.05$ for both). Multiple linear regression analysis indicated that age had no independent effect on total- or LDL-C ($P < 0.05$) in the group as a whole ($n = 141$) when menopausal status and adiposity (total body fat, central skinfolds or estimated IAF) were included in the model (data not shown in table form).

Discussion

We tested the hypotheses that, 1) menopause-related differences in plasma lipid-lipoprotein concentrations were associated with greater estimated intra-abdominal adiposity, and that, 2) the relationship between individual adipose depots and lipid-lipoproteins differed with menopausal status. We found that the increased estimated IAF among post- (vs pre-) menopausal women accounted, in large part, for the adverse lipid (total-C, LDL-C and triglycerides) profile of the former. We also found that the relationship between central skinfolds and LDL-C differed with menopausal status, being significant prior to, but not after, menopause.

Postmenopausal women had higher levels of total-C, LDL-C and triglycerides. An increase in LDL-C has been observed following menopause in other studies.³⁻⁵ Greater LDL-C may explain the greater total-C observed in the present study, although menopause is reported to increase VLDL-C as well.¹⁸ Higher LDL-C following menopause may be due, at least in part, to the decrease in estrogen and the associated decline in hepatic LDL receptor activity,¹⁹ effects of the menopausal transition that are independent of changes in fat distribution.

However the present results suggest that changes in fat distribution, specifically an increase in IAF, may explain in the higher total-C, LDL-C and triglyceride concentrations observed following menopause in this study and others.⁴ Deposition of IAF, due to its high sensitivity to catecholamine-induced lipolysis,^{20,21} can result in increased circulating lipids and lipoproteins.⁹ Non-esterified fatty acids mobilized from IAF into the portal circulation, may increase hepatic production of triglycerides and ApoB lipoprotein, and increase subsequent export of VLDL particles.²² Increased VLDL-triglycerides in turn can depress circulating concentrations of HDL-C due to the action of cholesterol-ester transfer protein.²³ In the present study, adjustment for estimated IAF decreased menopause-related differences in levels of total-C, LDL-C and triglycerides by approx 40–70%.

HDL-C was not associated with any component of body fat in either group of women. We expected HDL-C to be associated with estimated IAF and with triglyceride concentration, as has been documented in other studies.^{18,24} HDL-C was associated with

Table 3 Influence of central skinfolds and estimated intra-abdominal adipose tissue (IAF) on menopause-related differences in circulating lipid-lipoprotein concentrations

Dependent variable	Menopausal status	Unadjusted	Adjusted for central skinfolds	Adjusted for estimated IAF
Total cholesterol (mmol/L)	Pre-	4.7 ± 0.1	4.8 ± 0.1	4.9 ± 0.1
	Post-	5.5 ± 0.1***	5.4 ± 0.1***	5.4 ± 0.1**
LDL-C (mmol/L)	Pre-	2.7 ± 0.08	2.8 ± 0.1 ^a	2.8 ± 0.1
	Post-	3.4 ± 0.1***	3.2 ± 0.1**	3.2 ± 0.1**
Triglycerides (mmol/L)	Pre-	1.0 ± 0.04	1.0 ± 0.04	1.0 ± 0.06
	Post-	1.2 ± 0.06***	1.2 ± 0.06*	1.1 ± 0.06

Values given are geometric mean ± s.e.m. adjusted as indicated, for pre- and postmenopausal women; LDL-C = low-density lipoprotein cholesterol.

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

^aSignificant interaction of covariate with menopausal status ($P < 0.05$).

triglyceride concentration in both groups. The lack of association of HDL-C with estimated IAF among premenopausal women, may have been due to the relatively low amount of this adipose depot; despite the lack of significance, the r was relatively high (-0.21). However, the r value for this relationship among postmenopausal women was quite low (-0.07), suggesting a very poor relationship. Thus, we suggest that menopausal status may affect regulation of HDL-C through a mechanism that is independent of, and overshadows the contribution of, IAF (*via* its contribution to circulating triglycerides). An effect of menopausal status on HDL-C has been demonstrated in some studies,^{3,25} but results vary.²⁶

We observed a menopause-related difference in the relationship of central skinfolds to LDL-C. This observation suggests that the metabolism of central subcutaneous adipose tissue may vary with reproductive status. A higher lipid turnover in this depot prior to menopause, is suggested by results of *in vitro* and *in vivo* studies. Basal lipolysis is higher in isolated adipocytes obtained from the subcutaneous abdominal *vs* the intra-abdominal region of obese premenopausal women.²⁷ Sensitivity to norepinephrine-induced lipolysis is higher in subcutaneous abdominal adipose tissue obtained from pre- *vs* postmenopausal women.²⁸ In pre- but not postmenopausal women, abdominal subcutaneous fat is more sensitive than portal depots (omental, mesenteric) to noradrenaline-stimulated lipolysis *in vitro*.²⁸ Moreover, in premenopausal women, subcutaneous abdominal, but not splanchnic adipose tissue showed increased turnover *in vivo* when subjects were given epinephrine.²⁹ These menopause-related changes in the regulation of lipid metabolism are probably due to changes in circulating gonadal hormones.^{30–32}

Following menopause, women deposit more lipolytically-sensitive IAF,^{33–35} and less lipolytically-resistant^{36,37} gluteofemoral fat.^{5–7} We did not observe a difference in the slope of the relationship between IAF and lipids in pre- *vs* postmenopausal women (for example, Figure 2, a and b). Thus, IAF presumably has a similar contribution to the lipid-lipoprotein profile in both groups. The greater amount of IAF among post- (*vs* pre-) menopausal women may explain the adverse lipid profile observed in the former.

The observed relationships between regional adiposity and plasma lipids were independent of age. Age did not correlate with lipid parameters among premenopausal women, and correlated with total- and LDL-C, but not triglycerides, among postmenopausal women. Furthermore, when age, menopausal status and indices of adiposity were subject to multiple linear regression in the group as a whole ($n = 141$), only adiposity had an independent effect on total- and LDL-C. Therefore, in this group of healthy women aged 35–65 y, age appeared to influence lipids through adiposity and menopausal status. This conclusion is similar to that reached by Hunter *et al*¹⁸ in women aged 17–77 y, and complements data on men aged 21–77 y in whom age had no adiposity-independent effect on lipid-lipoprotein variables.³⁸

The role of IAF in menopause-related differences in CVD risk factors has been investigated by others. Zamboni *et al*³³ found that IAF, as measured with computed tomography, best predicted several indices of metabolic disorder in obese pre- and postmenopausal women ($n = 40$ and 17, respectively; stepwise multiple regression), but predicted triglycerides only in the latter group. Similarly, the present results (Table 2, a and b) suggested that estimated IAF only had an independent effect on triglycerides in the postmenopausal group. (This result should be considered tentative, however, given that the r for the relationship between estimated IAF and triglycerides did not differ with menopausal status). The presence of independent associations between IAF and metabolic parameters in the premenopausal women of Zamboni *et al*³³ may have been a result of the obesity status, and consequent greater visceral obesity, of the subjects (mean IAF of 151 ± 75 and 205 ± 60 cm² in pre- and postmenopausal women, respectively). Hunter *et al*¹⁸ reported that adjustment for IAF, age and physical activity, eliminated significant effects of menopausal status on most measured risk factors in a broad cross-section of women not selected for hormone use (age 17–77 y, $n = 220$). However, menopausal status had an independent effect on total cholesterol (as well as on the ratio of total- to HDL-C and on VLDL-C). An independent effect of menopausal status on total-C was also suggested by the present study (Table 3). Thus, the effect of

menopausal status on total cholesterol appears to involve factors that are independent of IAF.

Conclusion

The higher circulating total-C, LDL-C and triglyceride concentrations in post- vs premenopausal women were partly explained by the greater estimated IAF. The relationship between central skinfolds and LDL-C differed with menopausal status, only being significant within the premenopausal group. Since this study used estimated, rather than measured IAF, the present results should be confirmed with measurements of IAF determined by computed tomography scanning or magnetic resonance imaging.

It is well-documented that both menopause and IAF are associated with increased risk of CVD. Since deposition of central or intra-abdominal fat can be affected by aspects of lifestyle, such as physical activity,³⁹ alcohol consumption,⁴⁰ stress,⁴¹ and smoking,⁴² and therefore, to some extent, is preventable, knowledge of how this adipose depot affects the lipid profile in postmenopausal women warrants further research.

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