Temporal sequence of blood lipids and insulin resistance in perimenopausal women: the study of women’s health across the nation

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ABSTRACT

Introduction To explore the temporal relationship between blood lipids and insulin resistance in perimenopausal women.

Research design and methods The longitudinal cohort consisted of 1386 women (mean age 46.4 years at baseline) in the Study of Women’s Health Across the Nation. Exploratory factor analysis was used to identify appropriate latent factors of lipids (total cholesterol (TC); triglyceride (TG); high-density lipoprotein cholesterol (HDL-C); low-density lipoprotein cholesterol (LDL-C); lipoprotein A-I (LpA-I); apolipoprotein A-I (ApoA-I); apolipoprotein B (ApoB)). Cross-lagged path analysis was used to explore the temporal sequence of blood lipids and homeostasis model assessment of insulin resistance (HOMA-IR).

Results Three latent lipid factors were defined as: the TG factor, the cholesterol transport factor (CT), including TC, LDL-C, and ApoB; the reverse cholesterol transport factor (RCT), including HDL-C, LpA-I, and ApoA-I. The cumulative variance contribution rate of the three factors was 86.3%. The synchronous correlations between baseline TG, RCT, CT, and baseline HOMA-IR were 0.284, −0.174, and 0.112 (p<0.05 for all). After adjusting for age, race, smoking, drinking, body mass index, and follow-up years, the path coefficients of TG→HOMA-IR, CT→HOMA-IR, and RCT→HOMA-IR were 0.073, −0.028, and −0.058, respectively. The path coefficients of CT→TG and CT→IR were 0.112 and 0.031, respectively. The sensitivity analyses showed consistent results.

Conclusions These findings provide evidence that TG and the reverse cholesterol transport-related lipids are related with insulin resistance bidirectionally. The path coefficients of CT→TG and CT→IR were 0.078 and 0.031, respectively.

INTRODUCTION

Dyslipidemia and insulin resistance are common risk factors for cardiovascular diseases (CVD), and their prevalence has shown an increasing trend.1-3 Previous studies have found that 53.5% of patients with hypercholesterolemia have insulin resistance,4 and 67.1% of patients with diabetes will also suffer from dyslipidemia.5 The coexistence of dyslipidemia and diabetes significantly increases the risk of stroke.6 Epidemiologic studies have found that patients with insulin resistance and diabetes tend to have higher levels of total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and lower high-density lipoprotein cholesterol (HDL-C). Dyslipidemia is
one of recognized risk factors of insulin resistance and diabetes. However, clinical research studies found that the improvement of insulin resistance occurred before the change of blood lipids, suggesting that the insulin resistance might be the cause of dyslipidemia. Available data are inconsistent about the interplay between blood lipids and insulin resistance.

Nowadays, researchers have paid increasing attention to the impact of exposure on women’s health, especially those during menopause. The perimenopause, as a transitional period before menopause, is a critical window for women’s health management. Changes in hormones and endocrine system during menopause are closely associated with central body fat accumulation and weight gain. This abdominal obesity can contribute to the development of dyslipidemia and insulin resistance. To date, studies focused on the relationship between blood lipids and insulin resistance in perimenopausal women are limited. The Study of Women’s Health Across the Nation (SWAN) is a longitudinal cohort study that aims to explore the effects of environmental exposures, physical and psychological changes on women’s health, before and after menopause. The cross-lagged path analysis is a form of path analysis that simultaneously explores the temporal relationship between blood lipids and insulin resistance in perimenopausal women.

RESEARCH DESIGN AND METHODS

Subjects

The Study of Women’s Health Across the Nation (SWAN) is a multicenter, multiethnic, longitudinal study of midlife women in the USA. The baseline examination started in 1996 and included 3302 premenopausal women aged 42–52. Participants self-identified as African American (28%), Caucasian (47%), Chinese (8%), Hispanic (8%), or Japanese (9%), recruited from seven sites across the USA: Boston, Chicago, Detroit, Oakland, Los Angeles, Newark, and Pittsburgh.

The SWAN cohort has been followed up 16 times to date, the baseline and the first 10 visits have been made public. The inclusion criteria of this study included the following: (1) at least two follow-up records during perimenopausal period; (2) no missing value in the main variables such as blood lipids, insulin, blood glucose, age, race, body mass index (BMI), smoking, drinking, and so on. Meanwhile, we excluded participants with cancer, AIDS, and systemic lupus erythematosus, which could affect the function of the endocrine system, at baseline and follow-up; records with ambiguous menopausal status due to hormone replacement therapy or hysterectomy; records of taking hypolipidemic, hypoglycemic agents, and undergoing uterine or ovarian resection. According to the criteria mentioned above, we selected baseline, Visit 1, 3, 5, and 7 data from the cohort. A total of 1386 women (mean age 46.35 years at baseline) were included in the current study. The mean follow-up time was 3.5 (range=1.0–7.8) years. All subjects included were in the early or late perimenopausal period.

Study protocols were approved by the Institutional Review Board at each site, and all participants provided written informed consent at each study visit. More details of the SWAN protocol have been published.

Measurements

Common protocols were standardized and used by trained examiners across the seven sites. Information obtained by questionnaires included demographics (age, ethnicity, level of education and so on), female physiology, medical history, and behavioral lifestyles. Smokers were defined as current smoking. Drinkers were defined as drinking at least once a week.

Anthropometric and laboratory data were collected by clinical technicians. Standing height and weight were measured in light clothing without shoes. BMI was calculated as weight in kilograms divided by height in meters squared. All participants were required to collect venous blood in the morning after a fasting period of no less than 10 hours. Serum and plasma samples centrifuged were stored at −80°C and sent to specified laboratory for measurement. Laboratory indexes include fasting plasma glucose (FPG, mmol/L), insulin (uIU/ml), TC (mmol/L), TG (mmol/L), HDL-C (mmol/L), LDL-C (mmol/L), lipoprotein A-I (LpA-I, mg/dL), apolipoprotein A-I (ApoA-I, mg/dL), and apolipoprotein B (ApoB, mg/dL). FPG was measured within 2 hours. Insulin resistance was estimated by homeostasis model assessment of insulin resistance (HOMA-IR) with the HOMA2 calculator provided by the University of Oxford (https://www.dtu.ox.ac.uk/).

Statistical analysis

Characteristics of study variables of baseline and follow-up investigations were compared using generalized linear models for continuous variables and χ² statistics for categorical variables. TG and HOMA-IR were log-transformed for normal distribution. The cross-lagged path analysis, a specific form of path analysis, is a typical statistical approach that simultaneously examines reciprocal, longitudinal relationships among a set of intercorrelated variables. Using this model to explore the temporal relationship between blood lipids and insulin resistance in perimenopausal women would provide more insights for the prevention of CVD and type 2 diabetes in women.

In the longitudinal cohort of SWAN, the present study aims to examine the temporal relationship between blood lipids and insulin resistance in perimenopausal women.
age, race, smoking, drinking, BMI, and follow-up years in regression residual analyses and then were standardized by Z-transformation (mean=0, SD=1). The cross-lagged path coefficients ($\rho_1$ and $\rho_2$) were calculated based on the correlation matrix, using the structural equation modeling with the R package **Lavaan**. The validity of model fitting was assessed by root mean square residual (RMR) and comparative fit index (CFI). RMR<0.05 and CFI>0.90 suggests a relatively good fit to the observed data. The difference between $\rho_1$ and $\rho_2$ was tested using Fisher’s Z-test as described in previous studies.

We identified appropriate latent lipid factors based on exploratory factor analysis and medical knowledge, due to the high correlation between blood lipids. Three common latent lipid factors were determined according to the Kaiser-Harris criterion and Cattell scree test, as shown in online supplemental figure S2. Examination by principal factor extraction found that the eigenvalues of the three factors were all >1. The cumulative variance contribution rate of the three factors was 86.9% (15.8% for factor 1, 32.3% for factor 2, 38.2% for factor 3, respectively), as shown in online supplemental table S1. Cross-lagged path models of these latent lipid factors and HOMA-IR were constructed, with adjustment for age, race, smoking, drinking, BMI, and follow-up years. The pattern of the model with latent variable is depicted in figure 1. Additionally, we implemented power analysis of cross-lagged path models between latent lipid factors and HOMA-IR, using the R package **WebPower**.

As sensitivity analysis, three-wave cross-lagged path models were built. Participants with three or more perimenopausal follow-ups were selected from the dataset, and we used their first and last two follow-up records to construct the three-wave cross-lagged path model. In addition, because there was no information about physical activity in visit 7, we used data from baseline, visit 1, 3, and 5 to further adjust physical activity and estrogen in the two-wave model.

### RESULTS

Table 1 summarizes the characteristics of 1386 perimenopausal women at baseline and follow-up. There were 663 (47.84%) whites, 338 (24.39%) blacks, 150 (10.82%) Chinese, 169 (12.19%) Japanese, and 66 (4.76%) Hispanics. BMI, insulin, HOMA-IR, TC, TG, LDL-C, HDL-C, LpA-I, ApoAI, ApoB, and the proportion of drinking were significantly different between baseline and follow-up.

Table 2 shows the cross-lagged path analysis of single blood lipid and HOMA-IR, with adjustment for age, race, smoking, drinking, BMI, and follow-up years. The path coefficients of two directions between HDL-C, LpA-I, ApoAI, and HOMA-IR were $-$0.093 to $-$0.050 (p<0.05 for all), while the path coefficients of TC and HOMA-IR, LDL-C, and HOMA-IR were $-$0.035 to 0.008 (p>0.05 for all). The synchronous correlation between baseline TG and baseline HOMA-IR was 0.284 (p=0.001). The path coefficients of TG→HOMA-IR was 0.073 (p=0.004) and HOMA-IR→TG was 0.057 (p=0.006), and the difference...
between the two path coefficients was not significant (p=0.673). The significant path coefficients suggested a bidirectional relationship between these blood lipids and HOMA-IR. The path coefficient of baseline ApoB→follow-up HOMA-IR (ρ₁=0.051, p<0.05) was significant, while baseline HOMA-IR→follow-up ApoB (ρ₂<0.001, p=0.985) was not significant, indicating a unidirectional temporal sequence of ApoB and HOMA-IR.

Online supplemental figure S2 and online supplemental table S1 present the information about exploratory factor analysis. Three latent lipid factors (TG factor, reverse cholesterol transport factor and cholesterol transport factor) were determined, and the cumulative variance contribution rate of the three factors was 86.3%. TG was the main loading of a single factor, we named it TG factor. The cross-lagged path analysis of TG factor was same as the model of TG and HOMA-IR showed in table 2. The factor loadings of HDL-C, LpA-I, and ApoA-I were highest of the reverse cholesterol transport factor (RCT). These three lipids were involved in the procedure of transporting cholesterol from peripheral tissues to liver. Cholesterol transport factor (CT) was loaded with TG, LDL-C, and ApoB. In the human body, these blood lipids were involved in the procedure of transporting cholesterol to peripheral tissues, which is contrary to RCT.

Figure 1 illustrates the cross-lagged path analysis between RCT and HOMA-IR, with adjustment for age, race, smoking, drinking, BMI, and follow-up years. The synchronous correlation between baseline RCT and baseline HOMA-IR was −0.174 (p<0.05). The path coefficients of baseline RCT→follow-up HOMA-IR (ρ₁=−0.091, p<0.001) and baseline HOMA-IR→follow-up RCT (ρ₂=−0.058, p=0.002) were all significant. The difference between the two path coefficients was not significant (p=0.383). The tracking correlation coefficients of RCT and HOMA-IR between different panels in the model were 0.748 and 0.443 (p<0.05 for both). Model fitting parameters RMR and CFI were 0.028 and 0.985, respectively. Figure 2 illustrates the cross-lagged path analysis between CT and HOMA-IR. The synchronous correlation between baseline CT and baseline HOMA-IR was 0.112 (p<0.05). The path coefficients of baseline CT→follow-up HOMA-IR (ρ₁=0.301, p=0.206) and baseline HOMA-IR→follow-up CT (ρ₂=−0.298, p=0.133) were not significant. The tracking correlation coefficients of CT and HOMA-IR between different panels were 0.766 and 0.455 (p<0.05 for both). RMR and CFI were 0.044 and 0.982, suggesting a good fit to the data. Online supplemental table S4 presents the cross-lagged path

### Table 2: The cross-lagged path coefficients between blood lipids and HOMA-IR

<table>
<thead>
<tr>
<th>Lipids</th>
<th>Synchronous correlations (r₁)</th>
<th>Path coefficients</th>
<th>Autocorrelation coefficients</th>
<th>Goodness of model fit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ρ₁ (Lipid→HOMA-IR)</td>
<td>ρ₂ (HOMA-IR→Lipid)</td>
<td>Lipid</td>
<td>HOMA-IR</td>
</tr>
<tr>
<td>TG</td>
<td>0.284*</td>
<td>0.073*</td>
<td>0.057*</td>
<td>0.649</td>
</tr>
<tr>
<td>HDL-C</td>
<td>−0.195*</td>
<td>−0.057*</td>
<td>−0.066*</td>
<td>0.765</td>
</tr>
<tr>
<td>LpA-I</td>
<td>−0.095*</td>
<td>−0.058*</td>
<td>−0.093*</td>
<td>0.539</td>
</tr>
<tr>
<td>ApoA-I</td>
<td>−0.077*</td>
<td>−0.050*</td>
<td>−0.066*</td>
<td>0.549</td>
</tr>
<tr>
<td>TC</td>
<td>0.093*</td>
<td>0.008</td>
<td>−0.035</td>
<td>0.733</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.092*</td>
<td>0.007</td>
<td>−0.021</td>
<td>0.753</td>
</tr>
<tr>
<td>ApoB</td>
<td>0.176*</td>
<td>0.051*</td>
<td>&lt;0.001</td>
<td>0.735</td>
</tr>
</tbody>
</table>

The number of subjects, N=1386.

*P<0.05.

ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; CFI, comparative fit index; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; LpA-I, lipoprotein A-I; RMR, root mean square residual; TG, triglyceride.
coefficients between latent lipid factors and HOMA-IR in different races, and the results were basically consistent.

In sensitivity analysis, we constructed three-wave cross-lagged path models with latent variables to explore the impact of changes in the follow-up interval. A total of 722 women with three or more follow-ups were included. The characteristics of these participants at baseline and last two follow-ups are described in online supplemental table S2. The mean age at baseline was 45.71 years. The mean follow-up year of T2, T3 was 2.51 and 4.76 years, respectively.

Figure 3 shows the three-wave cross-lagged path model of RCT and HOMA-IR, with adjustment for the same covariates mentioned above. The path coefficients of RCT \( \rightarrow \) HOMA-IR \( T_2 \) (\( \rho_1 = -0.117, p = 0.001 \)), HOMA-IR \( T_1 \) \( \rightarrow \) RCT \( T_2 \) (\( \rho_2 = -0.055, p = 0.033 \)), RCT \( T_2 \) \( \rightarrow \) HOMA-IR \( T_3 \) (\( \rho_3 = -0.078, p = 0.030 \)), and HOMA-IR \( T_2 \) \( \rightarrow \) RCT \( T_3 \) (\( \rho_4 = -0.055, p = 0.025 \)) were all significant. These path coefficients suggest that there were bidirectional relationships between RCT and HOMA-IR in T1 \( \rightarrow \) T2 and T2 \( \rightarrow \) T3, consistent with the two-wave model in Figure 1. The differences between \( \rho_1 \) and \( \rho_2 \) (\( p = 0.236 \)) as well as \( \rho_3 \) and \( \rho_4 \) (\( p = 0.661 \)) were not significant.

Online supplemental figure S3 shows the three-wave cross-lagged path model of CT and HOMA-IR. The path coefficients between CT and HOMA-IR were not significant in neither T1 \( \rightarrow \) T2 or T2 \( \rightarrow \) T3. These findings were same as the model in Figure 2. Online supplemental figure S4 shows the three-wave cross-lagged path model of TG and HOMA-IR. The path coefficients between TG and HOMA-IR within T1 \( \rightarrow \) T2 were all significant, while T2 \( \rightarrow \) T3 were not all significant. The tracking correlation coefficients between different panels in three-wave models were all significant, and the model parameters were presented in online supplemental table S3. Online supplemental table S5 presents the power analysis of cross-lagged path models between latent lipid factors and HOMA-IR, and the powers of these models were all acceptable. Online supplemental table S6 shows the two-wave cross-lagged path models between latent lipid factors and HOMA-IR with further adjustment for physical activity and estrogen, and the results were basically consistent.

**DISCUSSION**

Despite the strong intercorrelation between blood lipids and insulin resistance has been well documented,16–21 the temporal relationship between them is not elucidated completely. The current study explored the temporal relationship between blood lipids and insulin resistance in a longitudinal cohort of perimenopausal women using cross-lagged path analysis. There was a bidirectional relationship between reverse cholesterol transport factor (HDLC, LpA-I, ApoA-I) and HOMA-IR. TG was also associated with HOMA-IR bidirectionally. In contrast, there was no temporal relationship between cholesterol transport factor (TC, LDL-C, ApoB) and HOMA-IR. Compared with the cholesterol transport process, the reverse process correlated to the regulation of glucose more closely.

In order to avoid the collinearity among blood lipids, three latent lipid factors (TG, RCT, CT) were identified based on the exploratory factor analysis. TG, as the most abundant lipid in human’s body, was examined as an independent factor in the current analysis. There was a bidirectional relationship between TG and HOMA-IR. The increase of TG or HOMA-IR will increase the level of each other. TG was widely used to predict the risk of insulin resistance and diabetes.22 23 Previous studies have shown that for 1-SD increase of TG, the insulin resistance in hepatic increased by 24%.24 Mendelian randomization analysis confirmed the causal effect of TG on insulin resistance.25 Elevated TG are frequently accompanied by elevated free fat acid (FFA), then the elevated FFA will affect insulin resistance through the glucose-fatty acid cycle.26 Glucose-fatty acid cycle, also called Randle cycle, refers to the significant reduction in the uptake and utilization of glucose that occurs in muscle when fatty acid oxidation is intense, accordingly, the insulin resistance may increase.25 26 Meanwhile, the effect of insulin resistance on TG has also been reported. An analysis of clinical intervention trials showed that metformin combined with lifestyle intervention could alleviate insulin resistance and reduce the level of TG in patients, and the effect to improve islet function appeared earlier than the effect to improve dyslipidemia.8 As the increase of insulin, the activity of lipoprotein lipase, which could decompose very low-density lipoprotein with plentiful TG, would decrease.27 In the three-wave cross-lagged path model, TG was associated with HOMA-IR unidirectionally between T2 and T3. This may be due to the small sample size, and the fact that the last two panels are closer to menopause, so the physical condition and
hormone regulation have changed. The deeper causes of this phenomenon need further research.

For reverse cholesterol transport factor, the present study identified it was bidirectionally linked to HOMA-IR. The increase in blood lipids of RCT can lead to a decrease in HOMA-IR, which is consistent with the findings of recent research studies.28 29 Studies showed that lower HDL-C was a risk factor for insulin resistance and diabetes. The risk of diabetes for people with low HDL-C was 2.2 times than that of normal individuals.28 Animal experiments reported alleviated insulin resistance after the injection of ApoA-I in pregnant rats.29 Physiological studies have shown that HDL-C could reduce the activity of gluconeogenic enzymes in the liver, accelerate the absorption of glucose, and alleviate the insulin resistance. Additionally, HDL-C could decrease the damage of IL-1, TNF-α, and other inflammatory factors on pancreatic β cells.30

The current analysis suggested that insulin resistance also had a negative effect on reverse cholesterol transport-related lipids. People with diabetes were often accompanied by lower levels of HDL-C and ApoA-I.30 31 Wang et al found that HDL-C decreased gradually as insulin resistance aggravated.32 Population-based study showed that, in the early stage of insulin resistance, the decomposition of ApoA-I increased by about 50%, compared with the control group.33 According to biochemical research, insulin resistance could result in increased TG and decreased HDL-C. Irregular metabolism of glucose might inhibit the synthesis of ApoA-I and reduce the activity of lecithin cholesterol acetyltransferase, which in turn led to a prolonged maturation of HDL-C.34

Previous studies have shown that cholesterol transport-related blood lipids were closely related to insulin resistance. Epidemiological evidence showed that elevated TC level was a risk factor for prediabetes and diabetes, and the risk of dyslipidemia in patients with insulin resistance was also increased significantly.7 35 36 Different from researches mentioned above, the current study found that there was no temporal relationship between the cholesterol transport factor and HOMA-IR. Additionally, TC and LDL-C were also independent with HOMA-IR. Though the significant path coefficient of baseline C was independent with insulin sensitivity.37 Prospective studies based on the Chinese population found that TG and LDL-C may not be risk factors for diabetes.38 American prospective analysis claimed that elevated insulin levels were not associated with the risk of hyperlipidemia.39 However, the mechanism between TC, LDL-C, ApoB, and HOMA-IR is not clear so far. Whether there is a causal relationship between cholesterol transport-related lipids and insulin resistance remains to be further studied.

**Strengths and limitations**

The current study has some important strengths. The analysis was based on the cross-lagged path model, a powerful method for dissecting the temporal sequences between intercorrelated variables, which could provide evidence for causal inference. Meanwhile, we included a lot of blood lipids and constructed models with latent variables. Integrating multiple information by latent variables could reduce the influence of strong correlations between variables. On the other hand, some limitations of the present study should be stated. The generalization of our conclusions is restricted because subjects included were perimenopausal women in this study. We could not ascertain the effect of menopause limited by the small sample size of menopausal participants. Though the covariates were adjusted, unknown confounders were not considered. Additionally, body fat distribution such as ectopic fat and visceral fat will change with the hormonal alterations of menopause;40 though we have adjusted BMI in the models, the effect of body fat is also worthy of further evaluation. However, there was no information about body fat in public dataset of SWAN. Studies with more information about body fat distributions are needed in the future to further examine these findings.

**CONCLUSION**

In conclusion, the current study demonstrated that TG and the reverse cholesterol transport-related lipids are related with insulin resistance bidirectionally, while there was no temporal relationship between the cholesterol transport factor (TG, LDL-C, ApoB) and insulin resistance. These findings supported the rationality of TG and HDL as components of metabolic syndrome and will provide recommendations for perimenopausal women to improve the quality of life and prevent the occurrence of dyslipidemia and diabetes. Further research focused on the interplay between dyslipidemia and diabetes should pay more attention to TG and lipids related with the reverse cholesterol transport process.

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Competing interests None declared.

Patient consent for publication Not applicable.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. The dataset supporting the conclusions of this article is available in a public, open access repository.

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