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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 (0.073, p=0.004), and HOMA-IR→TG (0.057, p=0.006) suggested a bidirectional relationship between TG and HOMA-IR. The path coefficients of RCT→HOMA-IR (−0.091, $P<0.001$) and HOMA-IR→RCT (−0.058, p=0.002) were also significant, but the path coefficients of CT→HOMA-IR (0.031, p=0.206) and HOMA-IR→CT (−0.028, p=0.113) were not. 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, while there is no temporal relationship between the cholesterol transport factor and insulin resistance.

Significance of this study

What is already known about this subject?

- Dyslipidemia and insulin resistance are common risk factors for cardiovascular diseases.
- Numerous studies have explored the coexistence of dyslipidemia and insulin resistance, but the temporal relationship between them is not well elucidated.

What are the new findings?

- We explored the temporal relationship between blood lipids and insulin resistance in a longitudinal cohort of perimenopausal women using cross-lagged path analysis.
- There were bidirectional relationships between TG as well as the reverse cholesterol transport factor (high-density lipoprotein cholesterol (HDL-C), lipoprotein A-I, apolipoprotein A-I) and insulin resistance in perimenopausal women.
- There was no temporal relationship between the cholesterol transport factor (total cholesterol, low-density lipoprotein cholesterol, apolipoprotein B) and insulin resistance.

How might these results change the focus of research or clinical practice?

- The conclusions supported the rationality of triglyceride and HDL as components of metabolic syndrome. These findings will provide a scientific recommendation for perimenopausal women to improve the quality of life and prevent the occurrence of dyslipidemia and diabetes.

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 the dyslipidemia and diabetes significantly increases the risk of stroke.[6] Epidemiologic studies have found that patients with insulin resistance and diabetes tended 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.[7] 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.[8] 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.[9] Changes in hormones and endocrine system during menopause are closely associated with central body fat accumulation and weight gain.[10 11] This abdominal obesity can contribute to the development of dyslipidemia and insulin resistance.[12 13] 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.[14] The cross-lagged path analysis is a form of path analysis that simultaneously examines reciprocal, longitudinal relationships among a set of intercorrelated variables.[15] 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.

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.[16] 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.[14]

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 χ^2 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 explores the temporal sequences of intercorrelated variables in the longitudinal study.[15] A conceptual version of the model is depicted in online supplemental figure S1. The path coefficient ρ_1 describes the effect of baseline Y_1 on the follow-up X_t, ρ_2 describes the effect of baseline X_1 on the follow-up Y_t in turn. The significance of path coefficient ρ_1 or ρ_2 indicates a clear temporal relationship. If ρ_1 and ρ_2 are both significant, it suggests a bidirectional relationship between X and Y. Before the cross-lagged path analysis, the values of indexes at baseline and follow-up were adjusted for

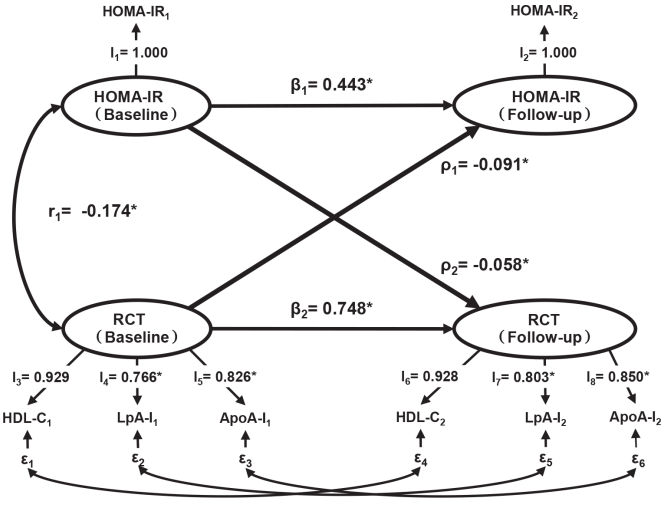

Figure 1 Cross-lagged path model between RCT and HOMA-IR, adjusted for age, race, smoking, drinking, BMI, and follow-up years. ρ_1 and ρ_2 are cross-lagged path coefficients; r_1 is synchronous correlation; β_1 and β_2 are tracking correlations; *p<0.05. ApoA-I, apolipoprotein A-I; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LpA-I, lipoprotein A-I; RCT, reverse cholesterol transport factor.

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 (ρ_1 and ρ_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).[17] RMR<0.05 and CFI>0.90 suggests a relatively good fit to the observed data. The difference between ρ_1 and ρ_2 was tested using Fisher's Z-test as described in previous studies.[18]

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 86.3% (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.

Table 1 Characteristics of the study cohort at baseline and follow-up

Variables	Baseline	Follow-up	P value*
Age (years)	46.3 (2.63)	49.8 (2.69)	<0.001
Smoker, n (%)	184 (13.3)	165 (11.9)	0.303
Drinker, n (%)	266 (19.2)	355 (25.6)	<0.001
BMI (kg/m^2)	27.3 (6.68)	28.1 (6.82)	0.003
FPG (mmol/L)	5.09 (0.61)	5.04 (0.70)	0.062
Insulin (uIU/mL)	10.1 (6.91)	10.9 (7.14)	0.002
HOMA-IR	2.36 (1.91)	2.54 (1.99)	0.015
TC (mmol/L)	4.97 (0.82)	5.20 (0.91)	<0.001
TG (mmol/L)	1.17 (0.59)	1.28 (0.67)	<0.001
HDL-C (mmol/L)	1.51 (0.36)	1.56 (0.39)	0.001
LDL-C (mmol/L)	2.92 (0.76)	3.05 (0.81)	<0.001
LpA-I (mg/dL)	49.3 (12.3)	53.9 (14.9)	<0.001
ApoA-I (mg/dL)	153.7 (25.3)	164.2 (27.7)	<0.001
ApoB (mg/dL)	106.0 (25.7)	109.9 (27.6)	<0.001

The number of subjects, N=1386.
Study variables are presented as mean (SD) or n (%).
*P value for the difference of variables between baseline and follow-up.
ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; BMI, body mass index; FPG, fasting plasma glucose; 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; TC, total cholesterol; TG, triglyceride.

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, HDL-C, LDL-C, LpA-I, ApoA-I, 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, ApoA-I, 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

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

	Synchronous correlations (r_1)	Path coefficients		Autocorrelation coefficients		Goodness of model fit	
		ρ_1 (Lipid→HOMA-IR)	ρ_2 (HOMA-IR→Lipid)	Lipid	HOMA-IR	RMR	CFI
TG	0.284*	0.073*	0.057*	0.649	0.415	0.054	0.930
HDL-C	−0.195*	−0.057*	−0.066*	0.765	0.425	0.017	0.993
LpA-I	−0.095*	−0.058*	−0.093*	0.539	0.431	0.014	0.995
ApoA-I	−0.077*	−0.050*	−0.066*	0.549	0.432	0.000	1.000
TC	0.093*	0.008	−0.035	0.733	0.435	0.028	0.979
LDL-C	0.092*	0.007	−0.021	0.753	0.436	0.021	0.989
ApoB	0.176*	0.051*	<0.001	0.735	0.427	0.035	0.969

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.

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 (ρ_1=0.051, p<0.05) was significant, while baseline HOMA-IR→follow-up ApoB (ρ_2<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 TC, 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 (ρ_1=−0.091, p<0.001) and baseline HOMA-IR→follow-up RCT (ρ_2=−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 (ρ_1=0.031, p=0.206) and baseline HOMA-IR→follow-up CT (ρ_2=−0.028, p=0.113) 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

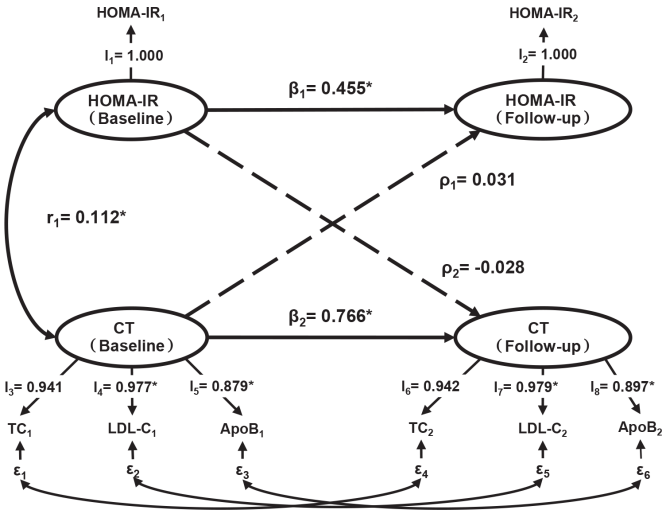

Figure 2 Cross-lagged path model between CT and HOMA-IR, adjusted for age, race, smoking, drinking, BMI, and follow-up years. ρ_1 and ρ_2 are cross-lagged path coefficients; r_1 is synchronous correlation; β_1 and β_2 are tracking correlations; *p<0.05. ApoB, apolipoprotein B; BMI, body mass index; CT, cholesterol transport factor; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

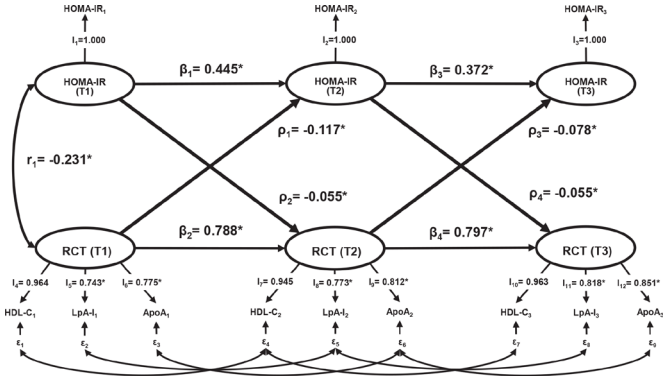

Figure 3 Cross-lagged path model between RCT and HOMA-IR in three panels, adjusted for age, race, smoking, drinking, BMI, and follow-up years. ρ_1, ρ_2, ρ_3, and ρ_4 are cross-lagged path coefficients; r_1 is synchronous correlation; β_1, β_2, β_3, and β_4 are tracking correlations; *p<0.05. ApoA-I, apolipoprotein A-I; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LpA-I, lipoprotein A-I; RCT, reverse cholesterol transport factor.

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_{T1}→$HOMA\text{-}IR_{T2}$ (ρ_1=−0.117, p=0.001), $HOMA\text{-}IR_{T1}$→RCT_{T2} (ρ_2=−0.055, p=0.033), RCT_{T2}→$HOMA\text{-}IR_{T3}$ (ρ_3=−0.078, p=0.030), and $HOMA\text{-}IR_{T2}$→RCT_{T3} (ρ_4=−0.055, p=0.025) were all significant. These path coefficients suggest that there were bidirectional temporal relationships between RCT and HOMA-IR in T1→T2 and T2→T3, consistent with the two-wave model in figure 1. The differences between ρ_1 and ρ_2 (p=0.236) as well as ρ_3 and ρ_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→T2 or T2→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→T2 were all significant, while T2→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,[19–21] 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 (HDL-C, LpA-1, ApoA-1) 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.[19] 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.[25] 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.[20 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 ApoB→follow-up HOMA-IR was relatively larger than that of TC and LDL-C but it did not influence the model of CT and HOMA-IR. The reasons for the inconsistency may be as follows. First, the levels of blood lipid and glucose in the population included in this study were lower than the patients with dyslipidemia or diabetes included in other studies. The difference in disease status may affect the relationship between blood lipids and HOMA-IR. Second, the present study that focused on perimenopausal women, gender difference and severe hormonal fluctuations during this period could be another explanation.

There is a lot of evidence to support our conclusion. A cross-sectional study showed that LDL-C was independent with insulin sensitivity.[37] Prospective studies based on the Chinese population found that TC 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 (TC, 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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Contributors WY, GZ, TZ, and GF generated the hypothesis, directed implementation, and wrote the manuscript. WY and GZ contributed to analytic strategy and statistical analyses. BF, CG, CL, JL, MW, and LH assisted with data validation and edited the manuscript. TZ, as guarantor, takes full responsibility for the work, including the study design, access to data, and the decision to submit and publish the manuscript.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The study was approved by the Public Health Ethics Committee, Shandong University (ID: 20190223). All participants provided written informed consent. For the SWAN study, institutional review board approval was obtained at each study site. Participants gave informed consent to participate in the study before taking part.

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SUPPLEMENTAL MATERIALS

Temporal Sequence of Blood Lipids and Insulin Resistance in Perimenopausal Women: The Study of Women's Health Across the Nation

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Supplement Table S1. Exploratory factor analysis of blood lipids

Blood Lipids	Factor 1	Factor 2	Factor 3
TG	0.958		
HDL-C		0.959	
LpA-I		0.720	
ApoA-I		0.831	
TC			0.954
LDL-C			0.988
ApoB			0.855
Eigen value	1.104	2.264	2.677
% of Variance	0.158	0.323	0.382

Supplement Table S2. Characteristics of the study cohort at baseline and last 2 follow-ups

Variables	Baseline (T1)	Follow-up 1 (T2)	Follow-up 2 (T3)
Age (years)	45.7 (2.37)	48.2 (2.51)	50.5 (2.45)
Smoker, n (%)	93 (12.9)	89 (12.3)	79 (10.9)
Drinker, n (%)	125 (17.3)	175 (24.2)	175 (24.2)
BMI (kg/m^2)	27.3 (6.73)	27.9 (6.73)	28.3 (6.88)
FPG (mmol/L)	5.09 (0.58)	5.07 (0.61)	5.03 (0.71)
Insulin (uIU/ml)	9.64 (6.10)	10.6 (6.59)	10.9 (7.00)
HOMA-IR	2.23 (1.58)	2.44 (1.77)	2.54 (1.91)
TC (mmol/L)	4.92 (0.80)	5.00 (0.83)	5.19 (0.90)
TG (mmol/L)	1.13 (0.56)	1.23 (0.63)	1.28 (0.66)
HDL-C (mmol/L)	1.49 (0.34)	1.53 (0.37)	1.55 (0.38)
LDL-C (mmol/L)	2.91 (0.74)	2.91 (0.75)	3.05 (0.80)
LpA-I(mg/dl)	48.4 (11.5)	50.7 (13.9)	55.1 (15.2)
ApoA-I(mg/dl)	151.2 (23.7)	158.9 (26.6)	165.4 (26.6)
ApoB(mg/dl)	105.2 (25.0)	107.1 (25.9)	109.5 (27.2)
Follow time (years)		2.51 (1.34)	4.76 (1.40)

The number of subjects, N = 722;

Study variables are presented as mean (SD) or n (%);

BMI, body mass index; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; LpA-I, lipoprotein A-I; ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B.

Supplement Table S3. Model fit of the three-wave cross-lagged path models of latent lipid factors and HOMA-IR

	Tracking Correlations (Latent Lipid Factor)		Tracking Correlations (HOMA-IR)		Goodness of Model Fit	
	T1→T2	T2→T3	T1→T2	T2→T3	RMR	CFI
CT ↔ HOMA-IR	0.791*	0.780*	0.470*	0.383*	0.065	0.919
RCT ↔ HOMA-IR	0.788*	0.797*	0.445*	0.372*	0.053	0.931
TG ↔ HOMA-IR	0.632*	0.707*	0.441*	0.356*	0.076	0.881

The number of subjects, N = 722;

*, $P < 0.05$

CT, Cholesterol transport factor (TC、LDL-C、ApoB); RCT, Reverse cholesterol transport factor (HDL-C、LpA-I、ApoA-I); HOMA-IR, homeostasis model assessment of insulin resistance;

RMR, root mean square residual; CFI, comparative fit index.

Supplement Table S4. The cross-lagged path coefficients between latent lipid factors and HOMA-IR in different races

	White (n = 729)				Others (n = 657)			
	ρ_1*	*P*	ρ_2†	*P*	ρ_1*	*P*	ρ_2†	*P*
CT ↔ HOMA-IR	0.032	0.346	-0.047	0.068	0.023	0.518	-0.023	0.346
RCT ↔ HOMA-IR	-0.083	0.020	-0.054	0.052	-0.098	0.006	-0.057	0.029
TG ↔ HOMA-IR	0.124	< 0.001	0.046	0.120	0.035	0.327	0.066	0.022

White: 663 whites and 66 Hispanics; Others: 338 blacks, 150 Chinese and 169 Japanese; CT, Cholesterol transport factor (TC、LDL-C、ApoB); RCT, Reverse cholesterol transport factor (HDL-C、LpA-I、ApoA-I); HOMA-IR, homeostasis model assessment of insulin resistance;

*, cross-lagged path coefficient of Lipid→HOMA-IR;

†, cross-lagged path coefficient of HOMA-IR→Lipid.

Supplement Table S5. Power analysis of cross-lagged path models between latent lipid factors and HOMA-IR

	Sample size	RMSEA	Significance level	Power
Two-wave model				
TG	1386	0.258	0.05	1.000
RCT	1386	0.073	0.05	1.000
CT	1386	0.105	0.05	1.000
Three-wave model				
TG	722	0.203	0.05	1.000
RCT	722	0.117	0.05	1.000
CT	722	0.169	0.05	1.000
Two-wave model in white participants				
TG	729	0.175	0.05	0.997
RCT	729	0.070	0.05	0.999
CT	729	0.108	0.05	1.000
Two-wave model in other participants				
TG	657	0.280	0.05	1.000
RCT	657	0.084	0.05	1.000
CT	657	0.102	0.05	1.000

TG, triglyceride factor; RCT, reverse cholesterol transport factor (HDL-C、LpA-I、ApoA-I); CT, cholesterol transport factor (TC、LDL-C、ApoB); HOMA-IR, homeostasis model assessment of insulin resistance;

RMSEA, root mean square error of approximation.

Supplement Table S6. The two-wave cross-lagged path models between latent lipid factors and HOMA-IR with further adjustment for physical activity and estrogen

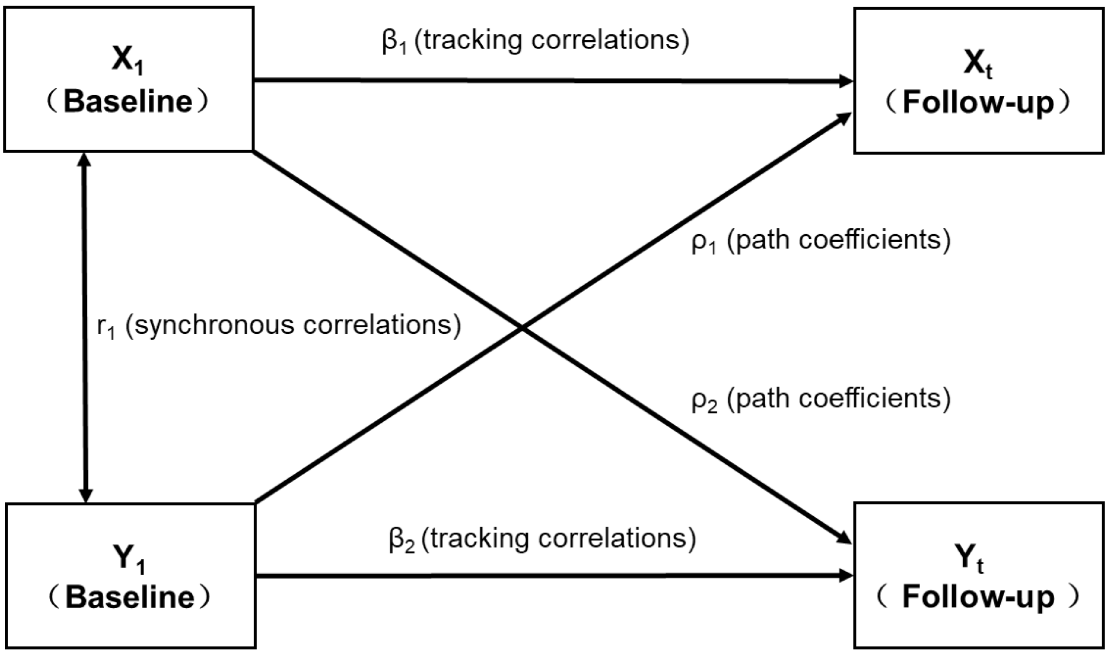
	ρ_1*	*P*	ρ_2†	*P*
CT ↔ HOMA-IR	0.032	0.194	-0.026	0.145
RCT ↔ HOMA-IR	-0.093	<0.001	-0.044	0.029
TG ↔ HOMA-IR	0.107	<0.001	0.041	0.051

Adjusted for age, sex, smoking, drinking, BMI, physical activity, estrogen and follow-up years;

CT, Cholesterol transport factor (TC、LDL-C、ApoB); RCT, Reverse cholesterol transport factor (HDL-C、LpA-I、ApoA-I); HOMA-IR, homeostasis model assessment of insulin resistance;

*, cross-lagged path coefficient of Lipid factor → HOMA-IR;

†, cross-lagged path coefficient of HOMA-IR → Lipid factor.

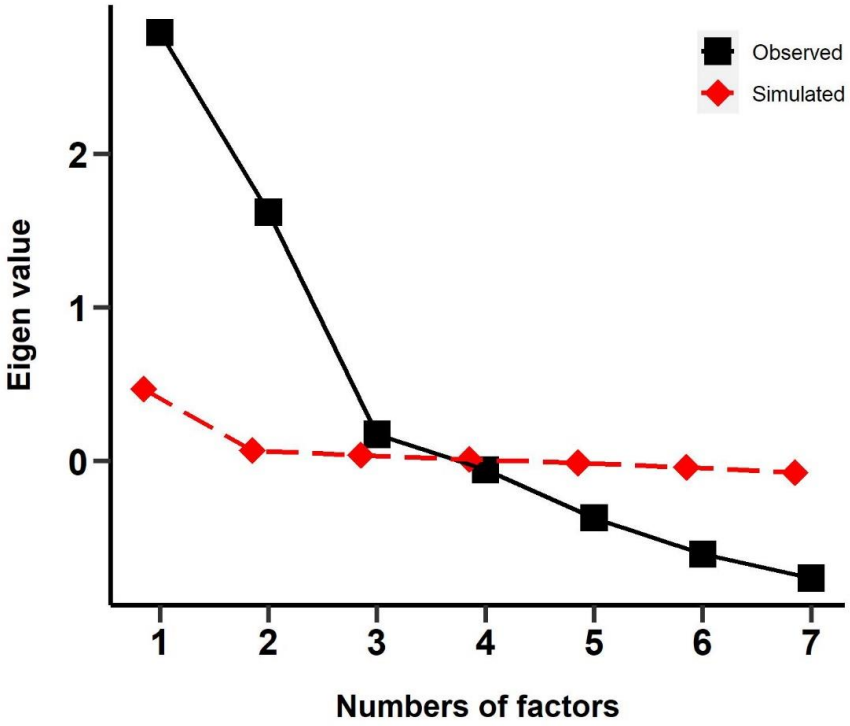


Supplement Figure S1. Cross-lagged path model

ρ_1 and ρ_2 are cross-lagged path coefficients;

r_1 is synchronous correlations;

β_1 and β_2 are tracking correlations.



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73 **Supplement Figure S2.** Scree plot of exploratory factor analysis

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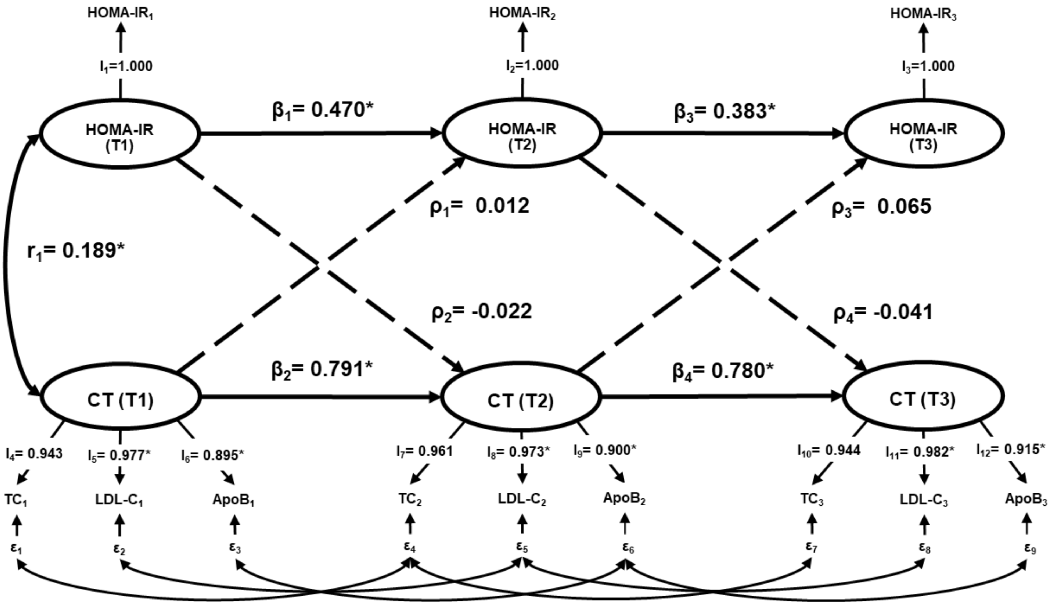


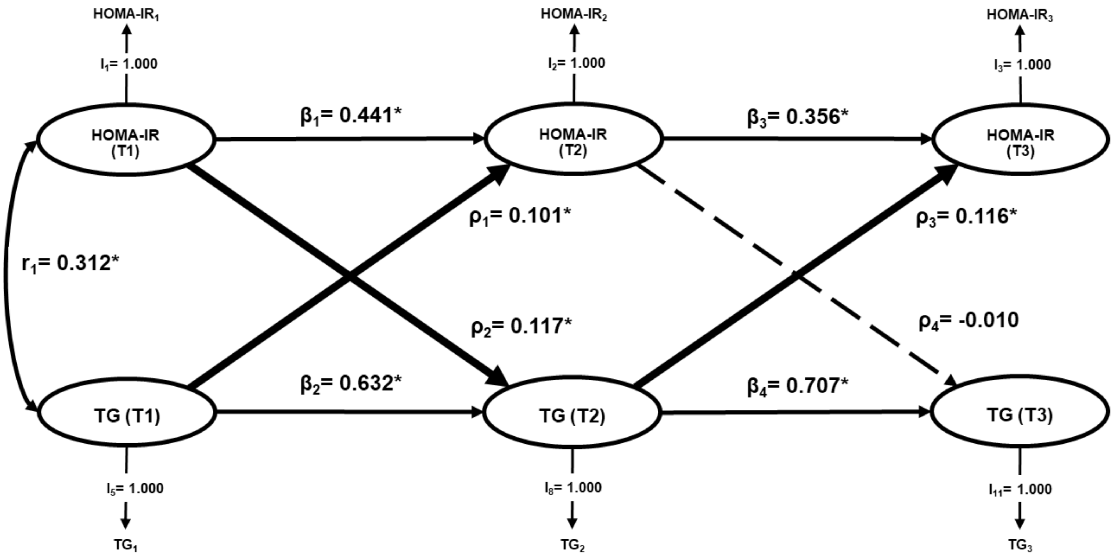
Supplement Figure S3. Cross-lagged path model between cholesterol transport factor (CT) and HOMA-IR in 3 panels, adjusted for age, sex, smoking, drinking, BMI and follow-up years.

ρ_1, ρ_2, ρ_3 and ρ_4 are cross-lagged path coefficients;

r_1 is synchronous correlation;

β_1, β_2, β_3 and β_4 are tracking correlations;

*, $P < 0.05$



Supplement Figure S4. Cross-lagged path model between triglyceride factor (TG) and HOMA-IR in 3 panels, adjusted for age, sex, smoking, drinking, BMI and follow-up years. ρ_1, ρ_2, ρ_3 and ρ_4 are cross-lagged path coefficients; r_1 is synchronous correlation; β_1, β_2, β_3 and β_4 are tracking correlations; *, $P < 0.05$