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

Wenhao Yu,1 Guangshuai Zhou,2 Bingbing Fan,1 Chaonian Gao,1 Chunxia Li,1 Mengke Wei,1 Jiali Lv,1 Li He,1 Guoshuang Feng,3 Tao Zhang1

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.

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
Metabolism

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.3 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.4 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 explores the temporal 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 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 tool 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 ρ₁ describes the effect of baseline Y₁ on the follow-up X₂, ρ₂ describes the effect of baseline X₁ on the follow-up Y₂ in turn. The significance of path coefficient ρ₁ or ρ₂ indicates a clear temporal relationship. If ρ₁ and ρ₂ 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
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 (ρ₁ and ρ₂) 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 ρ₁ and ρ₂ 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 86.3% (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.

### 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 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/m²) | 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.

---

**Figure 1** Cross-lagged path model between RCT and HOMA-IR adjusted for age, race, smoking, drinking, BMI, and follow-up years. ρ₁ and ρ₂ are cross-lagged path coefficients; rₛ is synchronous correlation; β₁ and β₂ are tracking correlations; *p<0.05. ApoA-I, apoliprotein 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.
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 (\(\rho_1=0.051\), p<0.05) was significant, while baseline HOMA-IR → follow-up ApoB (\(\rho_2=0.001\), 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, TC, LDL-C, and ApoA-I; 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; LpA-I, lipoprotein A-I; RMR, root mean square residual; TG, triglyceride).

The number of subjects, N=1386. *P<0.05.

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

| Synchronous correlations \((r_s)\) | Path coefficients | Autocorrelation coefficients | Goodness of model fit |
|-----------------------------------|-------------------|-----------------------------|----------------------|
|                                   | \(\rho_1\) (Lipid → HOMA-IR) | \(\rho_2\) (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                             | 0.082*             | 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 synchronous correlation between baseline RCT and HOMA-IR was −0.091 (p<0.001) and baseline HOMA-IR → follow-up RCT (\(\rho_2=0.058\), 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 (\(\rho_1=0.031\), p=0.206) and baseline HOMA-IR → follow-up CT (\(\rho_2=0.028\), 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.

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 (\(\rho_1=0.091\), p<0.001) and baseline HOMA-IR → follow-up RCT (\(\rho_2=0.058\), 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).
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 were 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 RCT1→HOMA-IR_2 (ρ_1=−0.117, p=0.001), HOMA-IR_1→RCT_2 (ρ_2=−0.055, p=0.033), HOMA-IR_2→RCT_3 (ρ_3=−0.078, p=0.030), and HOMA-IR_3→RCT_3 (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=0.256) 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, 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-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. Previous studies have shown that for 1-SD increase of TG, the insulin resistance in hepatic increased by 24%. Mendelian randomization analysis confirmed the causal effect of TG on insulin resistance. 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. 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. 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. As the increase of insulin, the activity of lipoprotein lipase, which could decompose very low-density lipoprotein with plentiful TG, would decrease. 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. 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 that of normal individuals. Animal experiments reported alleviated insulin resistance after the injection of ApoA-I in pregnant rats. 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.

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. Wang et al found that HDL-C decreased gradually as insulin resistance aggravated. 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. 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.

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. 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 HOMA-IR, which is consistent with the findings 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 perimenopausal 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; 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.

Author affiliations
1Department of Biostatistics, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, China
2Department of Human Resources, Zibo Central Hospital, Zibo, Shandong, China
3Big Data and Engineering Research Center, Beijing Children’s Hospital Capital Medical University, Beijing, China

Acknowledgements This study is a joint effort of many investigators and staff members and their contribution is gratefully acknowledged. We especially thank the staff, investigators, and participants who participated in SWAN.

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 perimenopausal 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; 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.
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, 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.

Funding This study was supported by grants from National Natural Science Foundation of China (grant no 81973147), Cheelo Young Scholars Program of Shandong University, Shandong University multidisciplinary research and innovation team of young scholars (2020QN0711), and YIT18034, Beijing University Capital Medical University Advanced Innovation Center for Big Data-Based Precision Medicine Plan (BHME-201901).

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.

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.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Ltd and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID id Tao Zhang http://orcid.org/0000-0003-1048-4443

REFERENCES

1. GBD 2017 Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the global burden of disease study 2017. Lancet 2018;392:1923–94.
2. Fox CS, Pencina MJ, Meigs JB, et al. Trends in the incidence of type 2 diabetes mellitus from the 1970s to the 1990s: the Framingham heart study. Circulation 2006;113:2914–8.
3. Kitz B, Kukulka E, Correll PD, et al. Prevalence of dyslipidemia and its control in type 2 diabetes: a multicenter study in endocrinology clinics of China. J Clin Lipidol 2016;10:150–60.
4. Luu S, Bao M-Y, Miao S-M, et al. Prevalence of hypertension, diabetes, and dyslipidemia, and their additive effects on myocardial infarction and stroke: a cross-sectional study in Nanjing, China. Ann Transl Med 2019;7:436.
5. von Eckardstein A, Schulte H, Assmann G. Risk for diabetes mellitus in middle-aged Caucasian male participants of the PROCAM study: implications for the definition of impaired fasting glucose by the American diabetes association. prospective cardiovascular Münster. J Clin Endocrinol Metab 2000;85:3101–8.
6. Wu R-R, Zhang F-Y, Gao K-M, et al. Metformin treatment of antipsychotic-induced dyslipidemia: an analysis of two randomized, placebo-controlled trials. Mol Psychiatry 2016;21:1537–44.
7. Stevenson JC, Hodis HN, Pickar JH, et al. Coronary heart disease and menopause management: the swinging pendulum of HRT. Atherosclerosis 2009;207:336–40.
8. Manderup CM, Egeland J, Nyberg M, et al. Effects of high-intensity training on cardiovascular risk factors in premenopausal and postmenopausal women. Am J Obstet Gynecol 2017;216:384–e1–384.e11.
9. Ramezani Tehrani F, Behboudi-Gandevani S, Ghanbarian A, et al. Effect of menopause on cardiovascular disease and its risk factors: a 9-year follow-up study. Climacteric 2014;17:164–72.
10. Ervin RB. Prevalence of metabolic syndrome among adults 20 years of age and over, by sex, age, race and ethnicity, and body mass index: United States, 2003–2006. Nati Health Stat Report 2008:1–7.
11. Després JP. Abdominal obesity: the most prevalent cause of the metabolic syndrome and related cardiometabolic risk. European Heart Journal Supplements 2006;8:S84–12.
12. Santoro N, Sutton-Tyrrell K. The Swan song: study of women’s health across the nation’s recurring themes. Obstet Gynecol Clin North Am 2011;38:417–23.
13. Hamaker EL, Kulpem RM, Grasman RRPP. A critique of the cross-lagged panel model. Psychol Methods 2015;20:102–16.
14. Sowers M, Crawford S, Sternfeld B. Swan: a multicenter, multithenic, community-based cohort study of women and the menopausal transition. J Clin Epidemiol 2000:175–88.
15. Jöreskog KG. Modeling development: using covariance structure models in longitudinal research. Eur Child Adolesc Psychiatry 1996;5 Suppl 1:88–18.
16. Agarwal T, Zhang H, Li Y, et al. Temporal relationship between childhood body mass index and insulin and its impact on adult hypertension: the Bogalusa heart study. Hypertension 2016;68:818–23.
17. al Muhtaseb N, al Yousef A, Bajaj JS. Apolipoprotein A-I, A-II, B, C-II, and C-III in children with insulin-dependent diabetes mellitus. Pediatrics 1992;89:936–41.
18. Bhowmik B, Siddiquee T, Mujumder A, et al. Serum lipid profile and its association with diabetes and prediabetes in a rural Bangladeshi population. Int J Environ Res Public Health 2018;15:1944.
19. Chien K, Cai T, Hsu H, et al. A prediction model for type 2 diabetes risk among Chinese people. Diabetologia 2009;52:443–50.
20. Karayiannis A, Willeit J, de Reck M, et al. Predicting the development of diabetes in older adults: the derivation and validation of a prediction rule. Diabetes Care 2005;28:404–8.
21. Grunnet LG, Laurila E, Hansson O, et al. The triglyceride content in skeletal muscle is associated with hepatic but not peripheral insulin resistance in elderly twins. J Clin Endocrinol Metab 2012;97:4571–7.
22. Randle PJ, Garland PB, Hales CN, et al. The glucose fatty-acid cycle. its role in insulin sensitivity and the metabolic disturbances of carbohydrate-mellitus. Lancet 1962;785–9.
23. Blanco A, Blanco G. Chapter 19 - Integration and Regulation of Metabolism. In: Blanco A, Blanco G, eds. Diabetes mellitus. Academic Press, 2017:425–45.
24. Ryan AS, Ortmeier HK. Insulin suppression of fatty acid skeletal muscle enzyme activity in postmenopausal women, and improvements in metabolic flexibility and lipoprotein lipase with aerobic exercise and weight loss. Int J Obes 2013;43:276–84.
25. Wilson PW, Meigs JB, Sullivan L, et al. Prediction of incident diabetes mellitus in middle-aged adults: the Framingham offspring study. Arch Intern Med 2007;167:1069–74.
26. Wu BJ, Sun Y, Ong K-L, et al. Apolipoprotein A-I protects against pregnancy-induced insulin resistance in rats. Arterioscler Thromb Vasc Biol 2019;39:1160–71.
27. Van Linthout S, Spillmann F, Schultheiss H-P, et al. High-dose lipoprotein at the interface of type 2 diabetes mellitus and cardiovascular disorders. Curr Pharm Des 2010;16:1504–16.
28. Finol M, Chinello GE, Contiero E, et al. Preliminary research on apolipoprotein A-I and A-II in patients with non-insulin-dependent diabetes mellitus (NIDDM). Haematologica 1993;78:277–81.
29. Wang F, Lu H, Liu F, et al. C-reactors are a liquid high-fat meal increases triglyceride levels but decreases high-density lipoprotein cholesterol in abdominally obese subjects with high postprandial insulin resistance. Nutr Res 2017;43:82–8.
30. Pont F, Duvaldi L, Florentin E, et al. High-Density lipoprotein apolipoprotein A-I kinetics in obese insulin resistant patients. An in vivo stable isotope study. Int J Obes Relat Metab Disord 2002;26:1151–8.
34 Lewis GF, Rader DJ. New insights into the regulation of HDL metabolism and reverse cholesterol transport. Circ Res 2005;96:1221–32.

35 Cui J, Sun J, Wang W, et al. Triglycerides and total cholesterol concentrations in association with IFG/IGT in Chinese adults in Qingdao, China. BMC Public Health 2018;18:444.

36 Rhee E-J, Han K, Ko S-H, et al. Increased risk for diabetes development in subjects with large variation in total cholesterol levels in 2,827,950 Koreans: a nationwide population-based study. PLoS One 2017;12:e0176615.

37 Slyper AH, Zvereva S, Schectman G, et al. Insulin resistance is not a major determinant of low-density lipoprotein particle size. Metabolism 1997;46:1275–80.

38 Han T, Cheng Y, Tian S, et al. Changes in triglycerides and high-density lipoprotein cholesterol may precede peripheral insulin resistance, with 2-h insulin partially mediating this unidirectional relationship: a prospective cohort study. Cardiovasc Diabetol 2016;15:154.

39 Haffner SM, Valdez RA, Hazuda HP, et al. Prospective analysis of the insulin-resistance syndrome (syndrome X). Diabetes 1992;41:715–22.

40 Milewicz A, Twarowska U, Demissie M. Menopausal obesity--myth or fact? Climacteric 2001;4:273–83.