

A Novel Use of Structural Equation Modeling to Examine Life-style and Cardio-metabolic Factors Associated With Micro-vascular Endothelial Dysfunction in Middle-aged Chinese Males

Ruijia Miao

Central South University Third Xiangya Hospital

Renhe Yu

xiangya school of public health, central south university

Hui Zhou

Central South University Third Xiangya Hospital

Lei Liu

Central South University Third Xiangya Hospital

jiangang wang (✉ 454258816@qq.com)

the third xiangya hospital <https://orcid.org/0000-0002-6122-6439>

Research

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Abstract

Objective: The present study aims to use structural equation modeling with multiple regression pathways to examine direct and indirect association of potential behavioral (diet, physical activity and sleep) and cardio-metabolic risk factors with micro-vascular endothelial dysfunction (ED) among middle-aged Chinese males.

Methods: The study was conducted in 306 middle-aged Chinese males, who underwent a health checkup between 2018 and 2019. Data on life-style behavior factors (physical activity, diet pattern, sleep quality, and diet data underwent exploratory and confirmatory factor analysis [EFA and CFA] in advance) and cardio-metabolic risk factors referring to metabolic syndrome [blood pressure, triglyceride (TG), fasting blood glucose, high-density lipoprotein cholesterol and body mass index] were introduced into the structural equation model to examine interrelationship among these factors and their association with ED, as evaluated by the reactive hyperemia index (RHI).

Results: Impaired ED defined by RHI <1.67 occurred in 39.2% of the participants. Both EFA and CFA identified two major dietary patterns: "prudent pattern" and "western pattern". The univariate test suggested that only TG and prudent dietary pattern were directly associated with RHI. Furthermore, prudent dietary pattern had a direct association with RHI ($\beta=0.16$, $P<0.05$) and an indirect association via triglyceride (Prudent diet→TG: $\beta=-0.15$, $P<0.05$; TG→RHI: $\beta=-0.17$, $P<0.001$). As to confirming the hypothesized association between variables apart, physical activity frequency was correlated to the decrease in TG ($\beta=-0.29$, $P<0.001$), but had no direct correlation to RHI.

Conclusion: The network of direct and indirect associations among life-style behavioral and cardio-metabolic risk factors with RHI measured ED among middle-aged males. The most significant modifiable factors identified were TG and prudent diet pattern, which needs to be targeted as preventive strategies for early micro-vascular impairment.

Background

Endothelial dysfunction (ED), which is a pathological condition characterized by an imbalance between endogenous vasodilating and vasoconstricting substances, is one of the earliest measurable markers of atherosclerosis¹, and a powerful predictor of future cardiovascular (CV) events². ED is usually a systemic disorder, but the small arteries could represent the basis for assessment of the functional capability of the micro-circulatory system due to their easy accessibility. Based on this principle, the reactive hyperemia-peripheral arterial tonometry (RH-PAT) located in the fingertips is a noninvasive signal technique, which is correlated to the endothelial function of microcirculation via measuring the flow response to hyperemia³. In light of the predictive value and easy detection, RH-PAT is suitable for health checkup populations for the prognostics of CV disease (CVD), and the risk factors of RH-PAT measured ED in this population are also worthy of study to prevent or recover ED.

If not all, the metabolic risk factors of CVD were generally associated with ED⁴. However, as to RH-PAT measured ED, there are controversies. Some correlations were found in specific populations. For instance, diabetic adolescents with poorly-controlled blood glucose had a worse ED reflected by lower the reactive hyperemia index (RHI) score of RH-PAT⁵. RHI was significantly lower in obese adolescents than in normal-weight adolescents^{6, 7}. A weak correlation was found between micro-vascular ED and body mass, and systolic and diastolic blood pressures, triglycerides (TG), high-density lipoproteincholesterol (HDL-c) and glucose in middle-aged men⁸. RHI was associated with blood pressure and HDL-c in chronic kidney disease and rheumatoid arthritis patients^{9, 10}. However, a negative profile also existed: RHI measured the micro-vascular ED, but failed to show the correlations with a risk factor profile (hypercholesterolemia, hypertension, diabetes, and overweight/obesity) in the asymptomatic population¹¹⁻¹³. In type-2 diabetic patients, the logarithmic-scaled RHI did not correlate with fasting plasma glucose, low-density lipoproteincholesterol and HDL-c, triglyceride levels, or systolic and diastolic blood pressures^{14, 15}.

In the present study, the investigators aimed to explore the association between metabolic risk factors and RH-PAT-measured ED. Furthermore, the behavioral factors were introduced to conceptualize a more advanced structure of predisposing factors of ED as a model. Since life-style behavior and cardio-metabolic factors are closely inter-related, an indirect relation among these might exist, rather than merely direct associations to ED. The investigators applied the statistical approach of structural equation modeling (SEM) to simultaneously analyze all relevant regression pathways, in order to better understand the role of these factors in the development of ED. Considering that age and gender are fixed factors and potentially exert significant effect on ED^{12, 16}, the investigators narrowed the population scale to middle-aged males to limit their affection on the counteracting effect of the present core factors.

By using SEM, the present study is the first to investigate the direct and indirect association of potential behavioral (diet, physical activity and sleep) and cardio-metabolic risk factors with RH-PAT-measured ED among middle-aged men.

Materials And Methods

Subject and design

A cross-sectional study was conducted. The medical records of 306 participants, who underwent a health check-up at the Health Examination Management Center of Third Xiangya Hospital from November 1, 2018, to August 31, 2019, were included. The inclusion criteria were males between 45 and 59 years old (WHO-recommended middle-aged group) underwent endothelial function examination. The exclusion criteria were symptomatic cardiovascular disease. The present study was conducted according to the principles expressed in the Declaration of Helsinki, and approved by the Ethics Committee of Third Xiangya Hospital. The consent form was signed by each participant.

Definitions And Measures

Systolic and diastolic blood pressure (SBP and DBP) was measured between 8 AM and 10 AM, following the guidelines from the American Health Association¹⁷. All measurements were conducted using an automatic digital BP monitor (Omron 9020). The participants were measured after a 10-minute rest period, with their feet straight upon the ground and their back and arm supported, and with the antecubital fossa at the level of the heart. The maximum cuff inflation was calculated by adding 30 mmHg to the pulse obliteration pressure, and the cuff was deflated at a constant rate of 2–4 mmHg per second. Venous blood was collected in the morning after overnight fasting. The serum samples were stored at 4 °C, and were subjected to testing (Hitachi 7170s autoanalyzer) within two days, according to the instruction of the analyzer. Fasting blood glucose (FBG), TG, and HDL-c were measured using the enzymatic method with the full-automatic biochemical analyser (Hitachi 7170s). The investigators chose to analyze five cardio-metabolic components of the metabolic syndrome as categorical risk factors: Body mass index (BMI), TG, HDL-c and FBG were categorized into three groups, according to the standards of the *Guidelines for prevention and control of overweight and obesity in Chinese adults (2004)*, and the *Guidelines on prevention and treatment of blood lipid abnormality in Chinese adults (2018)*: BMI (< 24–28 kg/m²), TG (< 1.70, 1.70–2.25, ≥ 2.26 mmol/L), HDL-c (< 1.04, 1.04–1.55, ≥ 1.55 mmol/L), FBG (< 6.1, 6.1–7.0, > 7.0 mmol/L or taking antidiabetic medication). Blood pressure was binary categorized as < 140/90 mmHg, ≥ 140/90 mmHg/or taking antihypertensive medication.

Data concerning diet, physical activity and sleep quality on the past one year were extracted from the "self-rated health measurement scale in health check-up" recommended by the Chinese Health Management Association¹⁸. This questionnaire was designed and administered by medical professionals, who collected data on the previous year. Physical activity was defined as moderate-intensity aerobic exercise, including fast walking, running, bicycle riding, rope skipping and swimming. All participants were assigned to categories, according the activity frequency per week (0 time, 1–2 times, 3–5 times, and > 5 times) and average duration each time (0 minute, < 30 minutes, and ≥ 30 minutes). Subjective evaluation of sleep quality was categorized into levels of poor, medium and excellent, according to the their own state of difficulty of falling sleep, early awakening, dreaminess, easily awaken, and shortened sleep duration. The 12 diet items in the scale included common diet behavior and diet habits: Anticipating dinner party per week (1. ≤ 1 time, 2. 2–3 times, 3. 4–5 times, and 4. ≥ 5 times); Midnight snack per week (1. never, 2. ≤ 1 time, and 3. > 1 time); Three meals on time per week (1. everytime, 2. failed 2–3 times, and 3. failed > 3 times); Times of milk and alcoholic drink per week (1. never, 2. 1–2 times, 3. 3–5 times, and 4. ≥ 6 times); Fruit, eggs and legume product per week (1. ≤ 2 times, 2. 3–5 times, and 3. ≥ 6 times); Vegetable per day (1. < 100 g, 2. 100–200 g, 3. > 200 g); Meat per day (1. < 50 g, 2. 50–100 g, and 3. > 100 g); Sugary beverage and coffee per week (1. never, 2. 1–2 times, and 3. ≥ 3 times).

ED was measured using the ENDOPAT™2000 device (Itamar Medical Ltd. Caesarea, Israel), which recorded the digital pulsatile volume changes without involving painful and risky invasive procedures. Micro-arterial tonometry signals were obtained from participants resting in the supine position in a quiet, temperature-controlled room after overnight fasting. Subjects were refrained from smoking and vigorous activity for 12 hours before the examination. Two finger probes were placed on one finger of each hand.

The baseline pulse amplitude was recorded during the first five minutes, followed by the 5-minute induction of ischemia induced by inflating upper-arm blood pressure cuff to 60 mmHg above systolic BP, with the opposite arm serving as a control, and the occlusion of blood flow was confirmed by the reduction of the ENDOPAT tracing to zero. After five minutes, the cuff was deflated, and the pulsatile tracing was recorded for another five minutes. RHI was automatically calculated using the computer algorithm of the ratio of the hyperemia and baseline pulse amplitude after control-arm correction. RHI < 1.67 was defined as ED.

Statistical analysis

Exploratory Factor Analysis (EFA)

EFA was first used to explore the latent construct of diet on 50% randomly selected responders. Principal Component Analysis followed by orthogonal Varimax rotation was conducted to estimate the factor loading, and determine the category and component of latent variables. Items of food and dietary habit with absolute factor loading of ≥ 0.30 entered the corresponding latent variable group. Only latent variables constructed with three or more items could be selected for further analysis to reduce measurement errors.

Confirmatory Factor Analysis (CFA)

Another 50% responders were analyzed. CFA was introduced to test the underlying construction of the food groups, and verify the latent construct explored by EFA.

Structural Equation Model (SEM)

Path analysis and structural modeling approach were used. First, the conceptual model that specified the correlations among dependent and independent variables is shown in Fig. 1. The apriori paths emanating from the measured univariate and unmeasured latent variables potentially direct or indirect affecting RHI-measured ED were constructed. The possible two-way correlation that implied two factors that were mutually connected were also given consideration. The SEM was fitted by the Maximum Likelihood Estimation method, the goodness-of-fit of the CFA and SEM. The chi-squared test (χ^2), normed chi-square test (χ^2/df), root mean square error of approximation (RMSEA), goodness-of-fit statistic (GFI), the adjusted goodness-of-fit statistic (AGFI), and the comparative fit index (CFI) were also evaluated to guarantee that the proposed model can be used. All analyses were conducted using IBM SPSS Statistics 21.0 and Amos version 23.0. P-values < 0.05 were considered statistically significant.

Chi-square tests were used to compare the frequency distribution of categorical data for metabolic risk factors. The factor score for each dietary pattern were calculated by weighting the consumption of each food item with the corresponding factor loading, and summing the resulting values. Then, the comparison between two groups evaluated by the factor score were made using student t-test.

Results

The mean age of the participants was 51.07 ± 3.98 years old, and the decrease in RHI was found in 39.2% of participants. All diet items were randomly incorporated into the Exploratory Factor Analysis on 50% of 306 participants. Four factors were extracted according to the PCA methods. The Kaiser-Meyer-Olkin (KMO) index was 0.64, and the assumption of sphericity was confirmed using Bartlette's test (Chi-Square = 425.884, DF = 66; P = 0.000). The Varimax rotated factor loadings are presented in Table 1, and the thresholds of absolute factor loading of each item, corresponding to common factors, were above 0.3. Factor 1 included five items, namely, fruit, legume product, milk, eggs, vegetable, and this was labeled as "Prudent dietary pattern". Factor 2 included three items, namely, dinner party, meat, alcoholic drink, and was labeled "Western dietary pattern". Factors three and four were eliminated for further CFA, since these contained only two items.

Table 1
Factor loading matrix for diet items using Exploratory Factor Analysis.

Items	Component			
	1	2	3	4
Fruit	0.672	-0.307	-0.134	-0.057
Legume product	0.641	0.070	0.036	-0.060
Milk	0.620	-0.111	0.274	0.090
Eggs	0.565	0.240	0.007	0.422
Vegetable	0.487	0.105	-0.461	0.111
Alcoholic drink	-0.156	0.719	0.197	-0.058
Dinner party	0.001	0.668	0.242	-0.145
Meat	0.087	0.666	-0.231	-0.103
Sugared beverages	-0.014	0.089	0.747	-0.192
Coffee	0.150	0.133	0.724	0.030
Night snack	0.043	0.214	0.115	-0.767
Three meals on time	0.077	-0.092	-0.060	0.749

Table 2 displayed the measurement model for "Prudent dietary pattern" and "Western dietary pattern," with observed variables previously recognized in EFA. CFA was used to test the reliability of the proposed grouping on the remaining 50% of participants. With the factor loading of each item in CFA still above 0.3, the measurement model of the "Prudent dietary pattern" and "Western dietary pattern" construct was

confirmed. The goodness of fit indices reported under Table 2 indicated an acceptable variance explanation and the good fit of two diet measurement models.

Table 2
Factor loading and reliability of identified factors verified by standardized regression weights of confirmatory factor analysis.

Prudent diet pattern		Western diet pattern	
Items	Factor loading	Items	Factor loading
Milk	0.40	Meat	0.35
Eggs	0.47	Alcoholic beverage	0.53
Fruits	0.59	Dinner party	0.55
Vegetable	0.44		
Legume products	0.52		
Fit indices of CFA model: $\chi^2 = 29.59$, DF = 20, $\chi^2/DF = 1.48$, p = 0.077, GFI = 0.954, AGFI = 0.918, CFI = 0.889, RMSEA = 0.056			

The Apriori SEM for evaluating the association of life-style behavioral and cardio-metabolic factors with RHI are depicted in Fig. 1. Table 3 indicates the behavioral and cardio-metabolic difference using the univariate analysis according to the presence of impaired RHI. Sleep quality, physical activity frequency and duration, western dietary pattern and most cardio-metabolic factors had no statistically difference between the groups, with or without RHI decrease. However, the prevalence of impaired RHI declined in participants with a lower TG and a higher factor score of prudent dietary pattern.

Table 3
Characteristics of participants according to the presence of ED

	RHI < 1.67 (n = 120)	RHI ≥ 1.67 (n = 186)	P
Activity frequency			
(times per week)			
0	41	65	0.089
1–2	34	32	
3–5	29	63	
≥ 5	16	26	
Activity duration (minutes each time)			
0	41	65	0.224
≤ 30	21	20	
≥ 30	58	101	
Sleep quality			
excellent	51	61	0.147
medium	55	92	
poor	14	33	
Blood pressure (mmHg)			
< 140/90	81	117	0.411
≥ 140/90 + medication	39	69	
BMI			
Normal	34	66	0.427
Overweight	62	86	
Obesity	24	34	
Triglyceride (mmol/L)			
≤ 1.7	46	112	0.001
1.7–2.26	31	30	
≥ 2.26	43	44	

	RHI < 1.67 (n = 120)	RHI ≥ 1.67 (n = 186)	P
HDL-c(mmol/L)			
< 1.04	18	22	0.213
1.04–1.55	87	127	
≥ 1.55	15	37	
Fasting blood glucose (mmol/L)			
< 6.1	89	142	0.546
6.1–7.0	16	27	
> 7.0	15	16	
Factor score			
Prudent diet pattern	-0.12 ± 0.06	0.08 ± 0.06	0.023
Western diet pattern	-0.01 ± 0.07	0.008 ± 0.06	0.829

The best-fit modified SEM was somewhat different from the hypothesized model (Fig. 2). Changes were made from the present hypothesized model, according to the crisis ratio (C.R) value. The investigators stepwise eliminated the paths with the unstandardized C.R lower than 1.5. The path coefficients on a one-way arrow among these multiple regression pathways supported the results of that univariate analysis, in which only TG and prudent dietary pattern were directly associated with RHI ($\beta = 0.16$, $P < 0.05$). Furthermore, RHI had an indirect association with prudent dietary pattern via TG (Prudent diet → TG: $\beta = -0.15$, $P < 0.05$; TG → RHI: $\beta = -0.17$, $P < 0.001$). As to confirming the hypothesized association between variables apart, physical activity frequency was negatively correlated to increased TG ($\beta = -0.29$, $P < 0.001$), but there was no direct correlation to RHI. It turned out that sleep quality and diet-related BP and BMI had no association with ED. Meanwhile, a two-way correlation was rebuilt in cardio-metabolic or behavior factors, according to the modification indices in covariance. The western diet pattern was not negatively correlated with prudent diet, but has an activity frequency. The model fit indices below Fig. 2 for SEM revealed that the tested model is generally qualified for fitting the data.

Discussion

To our knowledge, the present study presented the first examination of the direct and indirect effects of modifiable risk factors on ED using SEM. The appropriate fit required the original hypothesized model to undergo changes. After the elimination of factors that made no contribution, only TG and prudent dietary pattern were directly associated with RHI. Furthermore, RHI had an indirect association with prudent dietary pattern via TG. In the field of health management, risk prevention and management of

cardiovascular disease are vital important study topics, especially learning risk factors when diseases were detected at the earliest stage. Another more widely-applied macro-vascular ED measurement is flow-mediated dilation (FMD), which is estimated as the percent change of brachial artery diameter at maximal dilation during hyperemia, when compared with the baseline value. ED in the conduit arteries might be more important in subjects with existing atherosclerosis, while that in resistance small vessels might be an early indicator of arteriosclerosis risk^{19, 20}. However, there was no correlation found between FMD and RHI when the two parameters were simultaneously measured²¹. Thus, the risk factors of RHI-measured ED, as an early marker of vascular impairment, are still worth digging in relatively healthy populations when undergoing health checkups.

It turned out that only TG in the metabolic syndrome cluster was associated with micro-vascular ED in the present health-checkup population, which was inconsistent with part of the previous reports listed in the introduction section. On the surface, the observed effect size of each metabolic risk factors significantly varied in several populations from studies, including the present study. According to the heterogeneous effect of RHI-related risk factors, the investigators analyzed the potential causality, as follows: (1) the estimated ED burden of cardio-metabolic risk factors should be affected by intrinsic characteristics of specific population in the magnitudes of their effects. Indeed, the endothelium from populations with the stratification of age, gender, race, region and disease category had varied susceptibility to risk^{22–24}. The first four stratifications that referred to genetic background or physiological properties were complex and non-modifiable. Concerning disease background, most previous studies concerned populations with a certain cardio-metabolic disease or autoimmune disease, as mentioned in the introduction. When compare to subjects with diseases, the health-checkup population had a relatively narrow range of risk factor levels, which were supposed to be below their counterpart in the population under the pathological state. Thus, this would more unlikely reveal the correlation. Furthermore, unlike the present SEM with multiple regression pathways, most previous evaluations were univariate analyses without adequate adjustment. This might lead to inflated effect sizes. In addition, an interesting phenomenon was found: lowering BP and blood glucose using anti-hypertensive and anti-diabetic medications for weeks does not improve the RHI-measured ED^{25–28}, but the short-term lowering of TG using fenofibrate could²⁹, to some extent, do this. This signifies that high TG might be a more sensitive index, imposing a greater effect on the endothelium for a certain amount of time.

Regarding the life-style behavior concerning diet, physical activity and sleep quality, this is the first study that explored the effect of diet pattern on micro-vascular ED. It was observed that prudent diet consisted of recognized healthy food for the previous year that indirectly ameliorated the impairment of ED through lowering TG, had a direct beneficial effect. The underlying mechanism for this advantage of prudent diet might be the high levels of contained vitamins, since it has been proven that vitamin C, D and E restored the macro- or micro-vascular ED^{30–32}. With regard to specific food, the intake of blueberry acutely improved the peripheral arterial dysfunction, and this contained polyphenol metabolites that might account for this advantage³³. It remains unknown whether quality protein-contained milk, egg and legume are involved in ED improvement, and more explorations are needed. Indeed, in south of China,

although a traditional dinner party generally tends to consume all kinds of alcoholic beverage and plenty of meat, no previous data revealed the effect of alcohol and meat on RHI-measured micro-vascular ED. However, several studies that used the FMD index to evaluate the alcohol effect were controversial: chronic moderate to heavy alcohol consumption caused macro-vascular endothelial dysfunction in Asian men^{34, 35}, and even FMD was significantly smaller in light alcohol drinkers³⁶. Conversely, the consumption of moderate and high alcoholic beverages was independently associated with better FMD, when compared to no alcohol consumption^{37, 38}, especially when consuming red wine³⁹. In general, the high dietary intake of food rich in antioxidants, such as specific fruits, vegetables and red wine, has a positive effect in improving FMD and endothelial function⁴⁰. Thus, the diet pattern should be taken into account, and the food type should be further subdivided, when possible. Aerobic exercise provides cardiovascular benefits without doubt. A previous study reported that physical activity improves micro-vascular ED^{6, 41}. Furthermore, the present study suggested that this advantage might be mediated by TG reduction. However, other mediated factors should be further explored.

The limitations of the present study are, as follows: (1) The data was cross-sectional. Therefore, the present hypothesized pathway did not reflect the timing dimension and causality. (2) The self-reported life-style behavior data may also be subjectively affected by social desirability bias. That is, the participants are likely to over-report the "healthy" behaviors. (3) When making the factor analysis, the accepted value of general coefficients in latent construct, including factor loading and Cronbach's α test, were not as desirable as the standard threshold should be. This was due to the wide variations of food major groups. The diet was divided into broad categories. Thus, a highly closed inter-correlation was hard to achieve, but a similar category and factor analysis was previously been made^{42, 43}.

In conclusion, these present results revealed the network of direct and indirect associations among life-style behavioral (diet, physical activity and sleep) and cardio-metabolic risk factors with RH-PAT-measured ED among middle-aged men. The most significant modifiable factors identified were TG and prudent diet pattern, which needs to be targeted as a preventive strategy for early micro-vascular impairment.

List Of Abbreviations

ED

endothelial dysfunction; EFA:exploratory factor analysis; CFA:confirmatory factor analysis; TG:triglyceride; CVD:cardiovascular disease; RH-PAT:reactive hyperemia-peripheral arterial tonometry; HDL-c:high-density lipoprotein cholesterol, BMI:body mass index; FBG:fasting blood glucose; SEM:structural equation model;

Declarations

Ethics approval and consent to participate

The present study was conducted according to the principles expressed in the Declaration of Helsinki, and approved by the Ethics Committee of Third Xiangya Hospital. The consent form was signed by each participant.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

Competing interests

The authors declare that they have no conflict of interest.

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Authors' contributions

RJM conceptualized the paper, coordinated the study and wrote the manuscript. RHY conducted the statistical analyses and revised the article. HZ, and LL contributed to the design of the study, data collection, and revised the article. JGW secured funding, contributed to conceptualize the paper and the write of parts of the manuscript.

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Figures

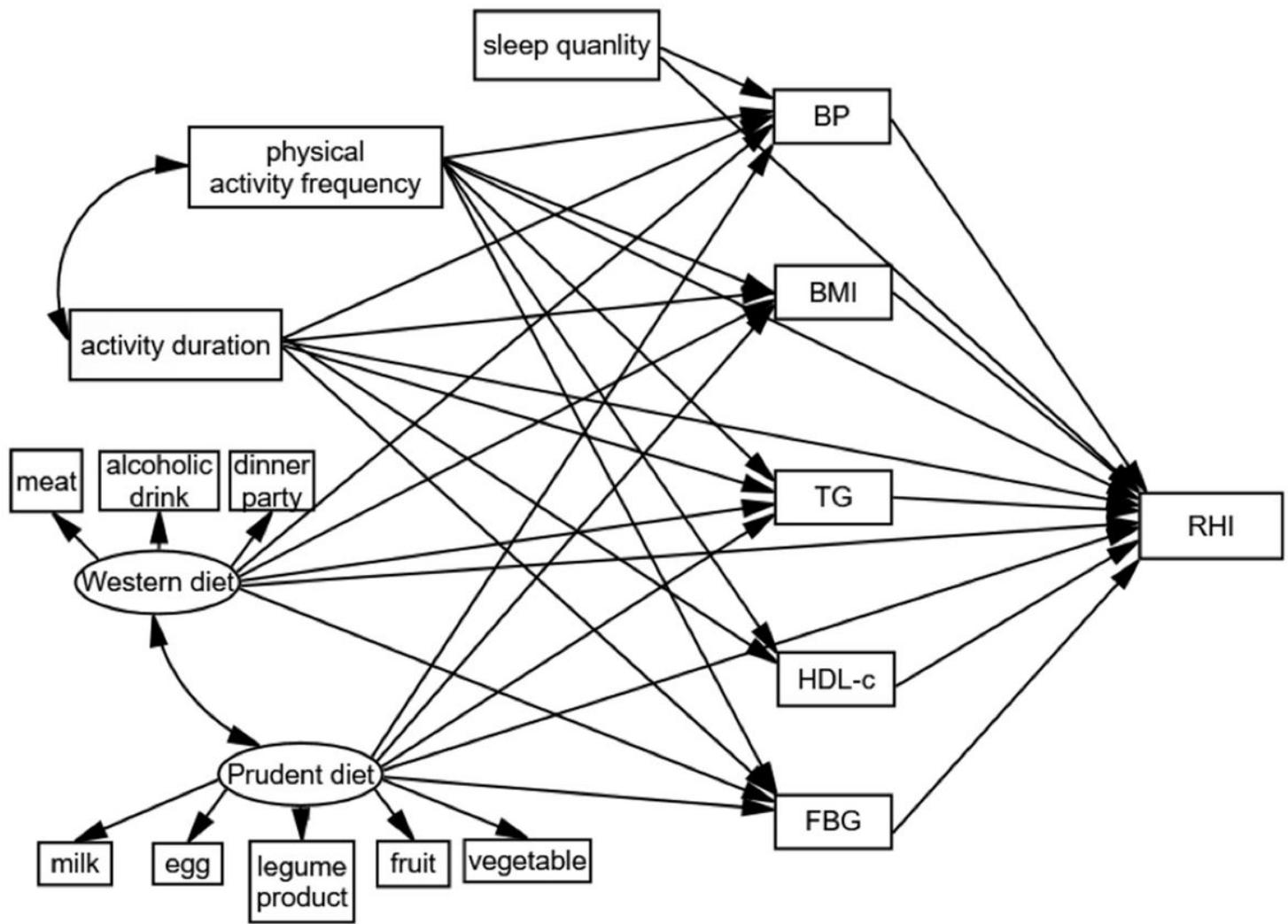


Figure 1

The structural model: Testing the association of life-style behavioral and cardio-metabolic factors with RHI.

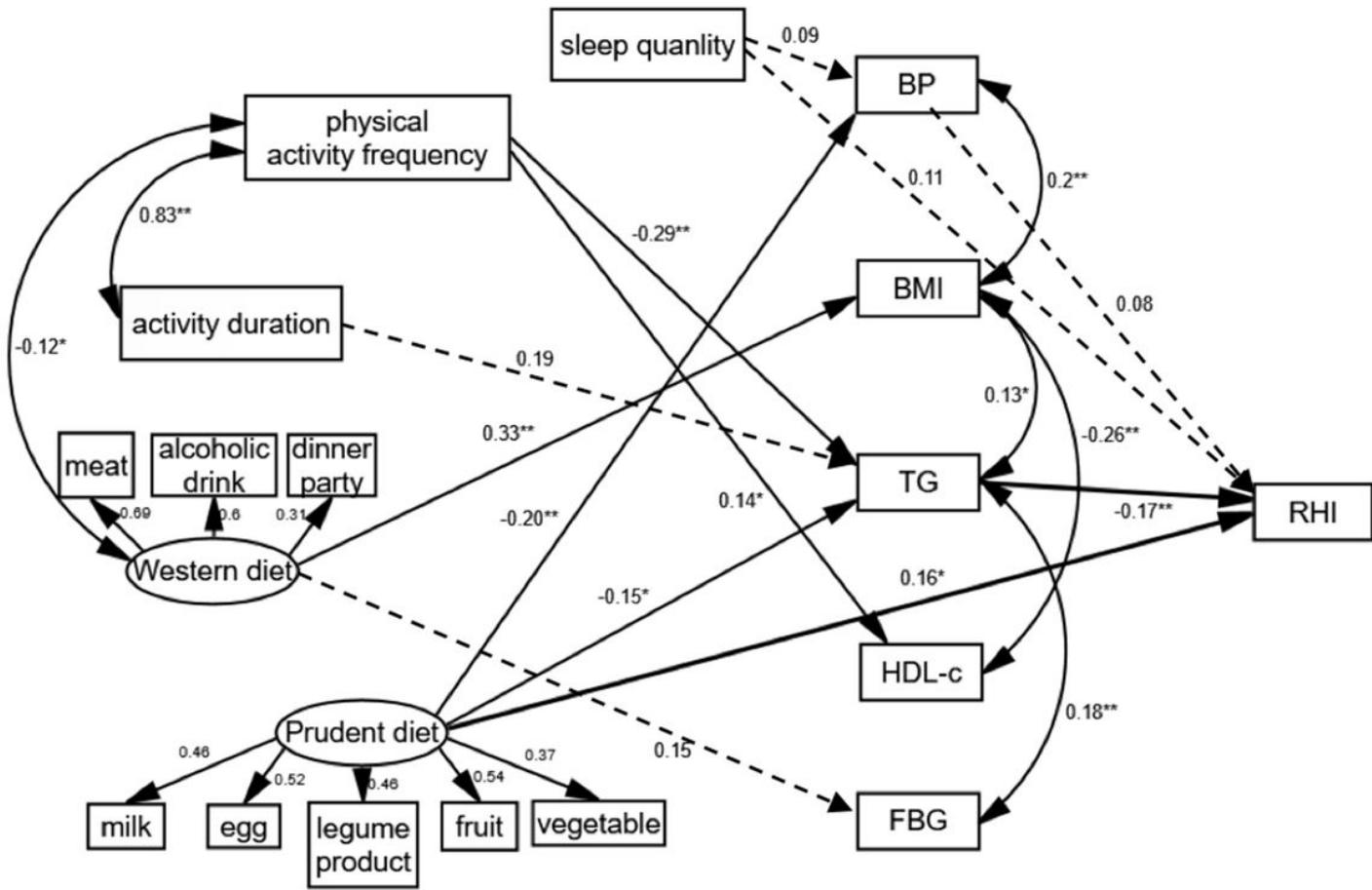


Figure 2

The final structural model indicating standardized regression weights after testing the association of life-style behavioral and cardio-metabolic factors with RHI. The fit indices were generally acceptable: $\chi^2 = 232.416$, DF = 110, $\chi^2/DF = 2.113$, p=0.000, GFI = 0.918, AGFI=0.886, CFI = 0.845, RMSEA=0.060. The solid-line pathway represented statistically important links with P<0.05, and the dashed lines means that the path has a crisis ratio of >1.5, but failed to pass the hypothesis tests with P≥0.05.

Supplementary Files

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