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Association Between Cumulative Average Lipoprotein Combined Index-Waist Circumference (LCI-WC) and Incident Cardiovascular Disease Among Middle-Aged and Older Chinese Adults: A Prospective CHARLS Cohort Study

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Article

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Abstract

Background

Cardiovascular disease (CVD) is a major public health burden among middle-aged and older adults in China. Dyslipidemia and central obesity jointly contribute to CVD risk, but the association between long-term cumulative exposure to composite lipid-abdominal obesity indicators and incident CVD remains unclear. This study examined whether cumulative average LCI-WC, defined using natural log-transformed lipoprotein combined index (LCI) and waist circumference, was associated with incident CVD.

Methods

Data were obtained from the China Health and Retirement Longitudinal Study (CHARLS). Cumulative average LCI-WC was calculated as the mean of LCI-WC values measured in 2011 and 2015, where LCI-WC was defined as ln(LCI)×waist circumference. Incident CVD was assessed at the 2018 follow-up. Logistic regression models and restricted cubic spline analyses were used to evaluate the association between cumulative average LCI-WC and incident CVD.

Results

A total of 4,597 participants were included, of whom 2,473 (53.8%) were women. The mean age was 58.4 (8.5) years. By the 2018 follow-up, 638 participants (13.9%) had developed incident CVD. In the fully adjusted model, each 1-SD increase in cumulative average LCI-WC was associated with a higher risk of incident CVD (OR, 1.137; 95% CI, 1.040–1.242). Compared with Q1, participants in Q4 had a higher risk of incident CVD (OR, 1.352; 95% CI, 1.041–1.755; P for trend = 0.023). Restricted cubic spline analysis suggested a positive linear association (P overall = 0.019; P for nonlinearity = 0.374).

Conclusions

Higher cumulative average LCI-WC was associated with increased odds of incident CVD among middle-aged and older Chinese adults. This composite index may provide additional epidemiological information for cardiovascular risk stratification

Introduction

Cardiovascular disease (CVD) remains one of the leading contributors to death and disease burden worldwide[1]. Early identification of individuals at elevated risk of CVD is therefore essential for chronic disease prevention and control. Dyslipidemia and central obesity are key metabolic risk factors implicated in the development and progression of CVD[2]. However, previous studies have not fully

captured the combined impact of atherogenic lipid burden and abnormal fat distribution. In recent years, composite metabolic indices incorporating lipid and obesity-related parameters, such as TyG-BMI, the lipid accumulation product (LAP), and the visceral adiposity index (VAI), have been widely used to assess atherosclerosis and CVD risk[3]. Evidence from population-based cohorts, including CHARLS, has shown that cumulative average TyG-BMI is associated with an increased risk of incident CVD among middle-aged and older adults[4]. Other studies have also suggested that LAP, VAI, and several nontraditional lipid indices may effectively reflect cardiometabolic risk[5]. The Lipoprotein combined index (LCI), derived from TC, TG, LDL-C, and HDL-C, integrates information on both elevated atherogenic lipids and reduced protective lipids. Previous studies have reported that LCI is closely associated with type 2 diabetes, fatty liver disease, and atherosclerosis-related phenotypes[6][7][8].

However, several important gaps remain in the existing literature. First, most previous studies have relied on metabolic indices measured at a single time point, which may not adequately capture the cumulative effects of prolonged exposure to abnormal lipid metabolism. Second, although LCI primarily reflects lipid metabolic burden, it does not directly incorporate central obesity, whereas waist circumference (WC), a simple anthropometric measure of abdominal obesity, is closely associated with CVD risk[9]. Therefore, combining LCI with WC may provide a more comprehensive assessment of cardiovascular risk arising from the joint effects of atherogenic dyslipidemia and central fat accumulation. Nevertheless, evidence regarding the association between cumulative average LCI-WC and incident CVD remains limited.

Based on this rationale, the present study used data from the 2011, 2013, 2015, and 2018 waves of the China Health and Retirement Longitudinal Study (CHARLS) to construct cumulative average LCI-WC for the period from 2011 to 2015. After excluding participants with CVD at baseline or during early follow-up, we evaluated the association between cumulative average LCI-WC from 2011 to 2015 and the risk of incident CVD in 2018. This study may help clarify the potential value of a composite lipid-central obesity index for CVD risk identification among middle-aged and older Chinese adults and provide epidemiological evidence for community-based early screening and metabolic risk stratification.

LCI-WC was defined as ln(LCI) x WC, where LCI was calculated as TC x TG x LDL-C / HDL-C, with lipid parameters expressed in mmol/L and WC expressed in cm. Although, to our knowledge, the construction of a cumulative average LCI-WC composite index based on natural log-transformed LCI has not been previously reported, this approach has a clear methodological rationale. First, the LCI-WC composite index simultaneously captures the combined metabolic burden of dyslipidemia and abdominal obesity, and previous studies have supported the joint contribution of central obesity and dyslipidemia to cardiovascular risk[10]. Second, because the original LCI is a multiplicative and ratio-based lipid index, it tends to have a markedly right-skewed distribution. Extreme values may strongly influence regression coefficients and cause model fitting to be disproportionately driven by a small number of outliers. Therefore, we applied natural logarithmic transformation to LCI before combining it with waist circumference to construct the log-transformed composite index LCI-WC, aiming to better characterize the association between this joint exposure and incident cardiovascular disease. Similar log-

transformation strategies have been widely used in established indices, such as the triglyceride-glucose index (TyG)[11] and the atherogenic index of plasma (AIP)[12].

Methods

2.1 Study Population

All data for this study were obtained from the China Health and Retirement Longitudinal Study (CHARLS), a nationally representative longitudinal survey of middle-aged and older adults in China. The study population included participants who were free of cardiovascular disease (CVD) during the 2011–2015 exposure assessment period. The exposure of interest was cumulative average LCI-WC, calculated from LCI-WC values measured in 2011 and 2015, and the outcome was incident CVD ascertained in 2018.

Inclusion and Exclusion Criteria: In the Wave 1 baseline survey conducted in 2011, the initial demographic sample included 17,705 participants. After applying the inclusion and exclusion criteria, 4,597 participants were included in the final analysis. The study size was determined by the number of eligible CHARLS participants who met the inclusion criteria and had available exposure and outcome information. No a priori sample size calculation was performed because this was a secondary analysis of an existing population-based cohort. Participants without required exposure measurements in 2011 or 2015, or without available CVD status at the 2018 follow-up, were excluded during sample selection. The participant selection process is shown in **Fig. 1**.

Figure 1. Flowchart of participant enrollment and follow-up. The flowchart shows the selection process of eligible participants from the CHARLS cohort. Participants with reported CVD during the 2011–2015 exposure assessment period, missing required exposure measurements, age < 45 years, extreme LCI or WC values, or incomplete 2018 CVD outcome data were excluded. CVD, cardiovascular disease; LCI-WC, lipoprotein combined index-waist circumference.

The CHARLS study was conducted in accordance with the Declaration of Helsinki and was approved by the Biomedical Ethics Review Committee of Peking University (IRB00001052-11015). Ethical approval for biomarker collection was granted under IRB00001052-11014. All participants provided written informed consent. This secondary analysis used de-identified CHARLS data, and the authors did not have access to information that could identify individual participants. Further details are available on the official CHARLS website (https://charls.pku.edu.cn/). This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement[13]. The CHARLS data used in this study were accessed on 20 March 2026.

2.2 Variable Definitions

Exposure variable: Cumulative average LCI-WC was calculated as the mean of LCI-WC values measured in 2011 and 2015, using the following formula:

Cumulative average LCI-WC = (LCI-WC2011 + LCI-WC2015) / 2

LCI-WC was calculated as:

LCI-WC = ln [TC (mmol/L) x TG (mmol/L) x LDL-C (mmol/L) / HDL-C (mmol/L)] x WC (cm)

Where TC, TG, LDL-C, HDL-C, and WC denote total cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and waist circumference, respectively. Because the original LCI, a multiplicative and ratio-based lipid index, showed a markedly right-skewed distribution (**Fig. 2**), natural logarithmic transformation was applied. The transformed index showed no evident right skewness.

Figure 2. Distribution of cumulative average LCI after multiple imputation(n = 4597). The histogram and box plot show the distribution of cumulative average LCI-WC among 4,597 participants. The dashed vertical lines indicate the mean and median values. LCI-WC, lipoprotein combined index-waist circumference.

Outcome variable: The outcome was incident cardiovascular disease (CVD), including incident heart disease and incident stroke. Participants were defined as having CVD if they self-reported a physician diagnosis of heart disease or stroke, or if they reported receiving disease-specific treatment for heart disease or stroke. Because exact dates of cardiovascular disease onset were not available in CHARLS, incident CVD was defined as CVD status assessed at Wave 4 in 2018 among participants who were free of CVD during the exposure assessment period, rather than as a time-to-event outcome.

Covariates: The following covariates were collected in this study: (1) demographic characteristics, including sex, age, educational attainment, and marital status; (2) clinical and anthropometric measurements, including systolic blood pressure (SBP), diastolic blood pressure (DBP), and waist circumference (WC); (3) lifestyle factors, including smoking status and alcohol consumption; (4) medical history and medication use, including hypertension, diabetes, kidney disease, liver disease, lipid-lowering treatment, antihypertensive treatment, and glucose-lowering treatment; and (5) laboratory measurements, including fasting blood glucose (FBG), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C).

Hypertension was defined as self-reported physician-diagnosed hypertension, use of antihypertensive treatment, or a mean SBP > = 140 mmHg or mean DBP > = 90 mmHg at baseline. Diabetes was defined as self-reported physician-diagnosed diabetes, use of glucose-lowering treatment, or baseline FBG > = 7.0 mmol/L. Other medical conditions were identified based on self-reported physician diagnosis or condition-specific treatment.

2.3 Missing Data Handling

Supplementary Fig. 1 illustrates the distribution of missingness across the observed variables. The proportion of missing data was low for all variables. To minimize information loss from complete-case

deletion and preserve the analytic sample size, multiple imputation was applied to handle missing covariate data.

Across the 24 covariates, there were 110,328 data cells, of which 317 were missing, corresponding to an overall missingness rate of 0.29%. At the variable level, missingness was generally low. The highest missingness rate was observed for dyslipidemia (2.11%), followed by BMI and diabetes (0.87% each), liver disease (0.65%), kidney disease (0.54%), and hypertension (0.52%); all other variables had missingness rates below 0.5%.

The imputation model included all covariates listed above, together with the cumulative average LCI-WC exposure and the 2018 incident CVD outcome, to preserve the correlation structure among the exposure, outcome, and covariates as much as possible. Because participants with missing data on the primary exposure or outcome had already been excluded during sample selection, imputation was performed only for missing covariate values.

Multiple imputation was conducted using the IterativeImputer method from the Python scikit-learn package. Five imputed datasets were generated, with a maximum of 10 iterations for each imputation procedure. Posterior sampling was used to account for imputation uncertainty. Categorical variables were numerically encoded before imputation and subsequently converted back to their original categorical or binary formats according to variable type. Baseline characteristics were summarized using the completed imputed dataset, and regression estimates were pooled according to Rubin's rules.

2.4 Statistical Analysis

The study population (n = 4,597) was categorized into four groups according to quartiles of cumulative average LCI-WC (Q1-Q4). Baseline demographic and clinical characteristics were summarized across LCI-WC quartiles. Continuous variables were expressed as the mean (standard deviation), and differences among groups were compared using one-way analysis of variance. Categorical variables were expressed as numbers (percentages), and differences among groups were assessed using the chi-square test.

To examine the association between cumulative average LCI-WC and the risk of incident cardiovascular disease, univariable and multivariable logistic regression models were fitted. The strength of the association was estimated using odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Model 1 was adjusted for age and sex. Model 2 was further adjusted for educational attainment, marital status, smoking status, and alcohol consumption. Model 3 included all covariates in Model 2 and was additionally adjusted for hypertension, diabetes, dyslipidemia, antihypertensive treatment, glucose-lowering treatment, lipid-lowering treatment, and estimated glomerular filtration rate (eGFR).

Multicollinearity was assessed using variance inflation factors (VIFs). The VIF for each variable included in the analysis was less than 5 (Supplementary Table 1), indicating no evidence of substantial multicollinearity. Multivariable-adjusted restricted cubic spline (RCS) logistic regression models were then used to evaluate the linearity and dose-response relationship between cumulative average LCI-WC

and incident cardiovascular disease, with four knots placed at the 5th, 35th, 65th, and 95th percentiles. In addition, subgroup and interaction analyses were performed to assess potential effect modification by age (< 60 vs. >=60 years), sex, smoking status, alcohol consumption, hypertension status, and diabetes status. All statistical analyses were conducted using R software (version 4.5.2).

2.5 Sensitivity Analyses

Four sensitivity analyses were conducted to assess the robustness of the main findings. First, a complete-case analysis was performed by refitting the logistic regression models after excluding participants with missing data for any variable. Second, propensity score matching was applied. The propensity score model included the same covariates as the fully adjusted model in the main analysis. A matched cohort was generated using 1:1 nearest-neighbor matching without replacement, with a caliper width of 0.01. Covariate balance between groups (Q1-Q2 vs. Q3-Q4) was considered acceptable when the standardized mean difference (SMD) was less than 0.10. Third, the original composite index without natural logarithmic transformation, WC x LCI, was analyzed to evaluate its association with incident cardiovascular disease. Fourth, an interaction term between LCI-WC and hypertension was added to the main model, and the P value for interaction was obtained using the likelihood ratio test.

Results

3.1 Baseline Characteristics of the Study Population

A total of 4,597 participants were included in the final analysis, including 2,473 women (53.8%) and 2,124 men (46.2%). The mean age was 58.4 (8.5) years. Baseline characteristics of the participants according to quartiles of cumulative average LCI-WC are shown in Table 1. The median (interquartile range) cumulative average LCI-WC among all participants was 216.6 (165.5, 274.1).

Compared with participants in the lowest quartile, those in higher quartiles of cumulative average LCI-WC showed significant differences in several baseline characteristics. First, cardiometabolic risk profiles tended to worsen with increasing LCI-WC quartiles. The prevalence of hypertension increased progressively from 11.9% to 32.4%, and the prevalence of diabetes was generally higher across increasing quartiles, despite slight fluctuations between groups (3.0%-6.8%). Second, lifestyle patterns differed significantly across LCI-WC quartiles. The proportions of current smoking and current alcohol consumption decreased as LCI-WC increased, whereas the proportions of former smoking and former alcohol consumption increased. These findings suggest that smoking and drinking status were associated with cumulative average LCI-WC. Third, regarding demographic characteristics, the proportion of women increased across LCI-WC quartiles, whereas age showed a slight decreasing trend ($P < 0.05$). No significant differences were observed in liver disease or kidney disease across groups.

The distribution of cumulative average LCI-WC is presented in **Supplementary Fig. 2**. Baseline characteristics stratified by incident cardiovascular disease status are summarized in **Supplementary Table 2**.

Table 1
Baseline characteristics of individuals classified by quartiles of cumulative average LCI-WC

Characteristics	Overall	Quartiles of the cumulative average LCI-WC				P-value
		Quartile 1	Quartile 2	Quartile 3	Quartile 4	
n	4597	1150	1149	1149	1149	
Gender (Female)	2473 (53.8%)	483 (42.0%)	623 (54.2%)	657 (57.2%)	710 (61.8%)	< 0.001
Age, years	58.4 ± 8.5	59.0 ± 9.0	58.3 ± 8.5	58.5 ± 8.5	57.8 ± 8.1	0.011
Education level						0.051
Illiterate	1312 (28.5%)	305 (26.5%)	355 (30.9%)	331 (28.8%)	321 (27.9%)	
Primary school	1898 (41.3%)	514 (44.7%)	468 (40.7%)	453 (39.4%)	463 (40.3%)	
Middle school or above	1387 (30.2%)	331 (28.8%)	326 (28.4%)	365 (31.8%)	365 (31.8%)	
Current married	4138 (90.0%)	1024 (89.0%)	1030 (89.6%)	1028 (89.5%)	1056 (91.9%)	0.096
SBP, mmHg	129.2 ± 20.7	124.3 ± 19.8	127.3 ± 20.2	130.4 ± 20.0	134.7 ± 21.3	< 0.001
DBP, mmHg	75.4 ± 11.8	72.2 ± 11.3	74.4 ± 11.3	76.3 ± 11.7	78.8 ± 12.1	< 0.001
BMI, kg/m²	23.5 ± 3.8	21.1 ± 2.9	22.8 ± 3.5	24.0 ± 3.7	26.1 ± 3.3	< 0.001
Waist circumference, cm	85.1 ± 9.5	78.0 ± 7.3	82.8 ± 8.1	86.7 ± 8.0	92.8 ± 8.0	< 0.001
Smoking status						< 0.001
Never	2856 (62.1%)	597 (51.9%)	710 (61.8%)	766 (66.7%)	783 (68.1%)	
Former	342 (7.4%)	92 (8.0%)	67 (5.8%)	88 (7.7%)	95 (8.3%)	
Current	1399 (30.4%)	461 (40.1%)	372 (32.4%)	295 (25.7%)	271 (23.6%)	
Drinking status						< 0.001
Never	2710 (59.0%)	583 (50.7%)	686 (59.7%)	699 (60.8%)	742 (64.6%)	
Former	336 (7.3%)	96 (8.3%)	72 (6.3%)	82 (7.1%)	86 (7.5%)	

Characteristics	Overall	Quartiles of the cumulative average LCI-WC				P-value
		Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Current	1551 (33.7%)	471 (41.0%)	391 (34.0%)	368 (32.0%)	321 (27.9%)	
Dyslipidemia	345 (7.5%)	33 (2.9%)	64 (5.6%)	94 (8.2%)	154 (13.4%)	< 0.001
Hypertension	937 (20.4%)	137 (11.9%)	195 (17.0%)	233 (20.3%)	372 (32.4%)	< 0.001
Diabetes	202 (4.4%)	35 (3.0%)	32 (2.8%)	57 (5.0%)	78 (6.8%)	< 0.001
Liver disease	154 (3.4%)	47 (4.1%)	46 (4.0%)	32 (2.8%)	29 (2.5%)	0.072
Kidney disease	252 (5.5%)	72 (6.3%)	67 (5.8%)	59 (5.1%)	54 (4.7%)	0.356
Lipid-lowering treatment	173 (3.8%)	13 (1.1%)	31 (2.7%)	40 (3.5%)	89 (7.7%)	< 0.001
Antihypertensive treatment	694 (15.1%)	87 (7.6%)	138 (12.0%)	174 (15.1%)	295 (25.7%)	< 0.001
Hypoglycemic treatment	134 (2.9%)	26 (2.3%)	20 (1.7%)	28 (2.4%)	60 (5.2%)	< 0.001
FBG, mmol/L	6.0 ± 1.8	5.7 ± 1.4	5.8 ± 1.4	6.1 ± 2.1	6.5 ± 2.2	< 0.001
TC, mmol/L	4.9 ± 0.9	4.4 ± 0.8	4.8 ± 0.8	5.1 ± 0.8	5.5 ± 0.9	< 0.001
TG, mmol/L	1.2 (0.8, 1.7)	0.8 (0.6, 1.0)	1.0 (0.8, 1.3)	1.3 (1.0, 1.7)	2.0 (1.5, 2.6)	< 0.001
HDL-C, mmol/L	1.3 ± 0.4	1.6 ± 0.4	1.4 ± 0.3	1.2 ± 0.3	1.1 ± 0.3	< 0.001
LDL-C, mmol/L	3.0 ± 0.9	2.5 ± 0.6	2.9 ± 0.7	3.2 ± 0.8	3.4 ± 1.1	< 0.001
eGFR, mL/min/1.73 m²	93.4 ± 13.6	94.7 ± 13.1	93.9 ± 13.5	92.6 ± 13.4	92.2 ± 14.3	< 0.001
LCI	13.5 (8.0, 23.3)	5.7 (4.4, 7.0)	10.5 (9.0, 12.8)	17.4 (14.4, 21.2)	32.2 (25.0, 41.2)	< 0.001
Cumulative average LCI-WC	216.6 (165.5, 274.1)	133.9 (110.6, 150.8)	191.3 (180.1, 204.1)	243.6 (230.4, 258.2)	312.9 (290.3, 340.7)	< 0.001

3.2 Association Between Cumulative Average LCI-WC and Incident Cardiovascular Disease

By the Wave 4 follow-up in 2018, 638 participants who were free of CVD during the exposure assessment period had developed incident CVD. Both the number and proportion of incident cardiovascular disease cases increased across quartiles of cumulative average LCI-WC (**Fig. 3**), with 119 cases (10.3%) in Q1, 154 (13.4%) in Q2, 181 (15.8%) in Q3, and 184 (16.0%) in Q4.

Figure 3. Incidence of cardiovascular disease by quartile of cumulative average LCI-WC (Q1–Q4). Bars show the proportion of participants with incident CVD in 2018 across quartiles of cumulative average LCI-WC. Q1-Q4 indicate increasing quartiles of cumulative average LCI-WC. CVD, cardiovascular disease; LCI-WC, lipoprotein combined index-waist circumference.

After adjustment for multiple covariates, the fully adjusted logistic regression model showed that higher quartiles of cumulative average LCI-WC were associated with greater odds of incident cardiovascular disease (Table 2). When cumulative average LCI-WC was modeled as a continuous variable, each 1-SD increase was significantly associated with higher odds of incident cardiovascular disease (OR, 1.137; 95% CI, 1.040–1.242).

Table 2
Association between cumulative average LCI-WC and incident cardiovascular disease.

Cumulative average LCI-WC	**Quartiles***				**P for trend**	**Continuous Per 1-SD increase**
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**		
Median	133.9	191.3	243.6	312.9	-	-
Number of cases, n(%)	119 (10.3%)	154 (13.4%)	181 (15.8%)	184 (16.0%)	-	-
Crude OR(95% CI)	Reference	1.341 (1.040–1.730)	1.620 (1.265–2.075)	1.652 (1.291–2.114)	< 0.001	1.223 (1.125–1.330)
Model 1, OR(95% CI)	Reference	1.334 (1.032–1.723)	1.596 (1.244–2.049)	1.640 (1.277–2.107)	< 0.001	1.221 (1.121–1.329)
Model 2, OR(95% CI)	Reference	1.345 (1.041–1.739)	1.588 (1.236–2.040)	1.613 (1.254–2.073)	< 0.001	1.212 (1.112–1.319)
Model 3, OR(95% CI)	Reference	1.298 (1.002–1.681)	1.499 (1.163–1.932)	1.351 (1.041–1.754)	0.023	1.137 (1.040–1.242)

Model 1: adjusted for age and sex. Model 2: additionally adjusted for education level, marital status, smoking, and alcohol consumption. Model 3: additionally adjusted for hypertension, diabetes, dyslipidemia, antihypertensive treatment, antidiabetic treatment, lipid-lowering treatment, and eGFR. *Quartile cut-points for cumulative average LCI-WC were 165.5, 216.6, and 274.1.

Restricted cubic spline (RCS) analysis was further performed (**Fig. 4**). After adjustment for all covariates, cumulative average LCI-WC showed a significant overall association with the risk of cardiovascular

disease (P overall = 0.019), with no evidence of significant nonlinearity (P for nonlinearity = 0.374). These findings suggest an approximately linear dose-response relationship between cumulative average LCI-WC and cardiovascular disease risk. The RCS analysis further supported the independent association between cumulative average LCI-WC and incident cardiovascular disease.

Figure 4. Association between cumulative average LCI-WC and incident cardiovascular disease. Restricted cubic spline analysis was used to evaluate the association between cumulative average LCI-WC and incident CVD. The solid line represents the adjusted odds ratio, and the shaded area represents the 95% confidence interval. The model was adjusted for age, sex, education level, marital status, smoking status, alcohol consumption, eGFR, hypertension, diabetes, dyslipidemia, antihypertensive treatment, antidiabetic treatment, and lipid-lowering treatment. CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; LCI-WC, lipoprotein combined index-waist circumference

When the composite outcome was further separated into incident heart disease and incident stroke, cumulative average LCI-WC showed a significant and approximately linear association with incident stroke, whereas the association with incident heart disease was weaker (**Fig. 5**).

Figure 5. Association between cumulative average LCI-WC and incident heart disease (left) and incident stroke (right). Restricted cubic spline analyses were used to evaluate the associations of cumulative average LCI-WC with incident heart disease and incident stroke. The solid lines represent adjusted odds ratios, and the shaded areas represent 95% confidence intervals. Models were adjusted for age, sex, education level, marital status, smoking status, alcohol consumption, eGFR, hypertension, diabetes, dyslipidemia, antihypertensive treatment, antidiabetic treatment, and lipid-lowering treatment. eGFR, estimated glomerular filtration rate; LCI-WC, lipoprotein combined index-waist circumference.

The model was adjusted for age, sex, education level, marital status, smoking, alcohol consumption, renal function (eGFR), hypertension, diabetes, dyslipidemia, antihypertensive treatment, antidiabetic treatment, and lipid-lowering treatment.

The model was adjusted for age, sex, education level, marital status, smoking, alcohol consumption, renal function (eGFR), hypertension, diabetes, dyslipidemia, antihypertensive treatment, antidiabetic treatment, and lipid-lowering treatment.

3.3 Subgroup Analysis

To further evaluate the association between cumulative average LCI-WC and incident cardiovascular disease, a series of subgroup analyses were performed (**Fig. 6**). Among the examined subgroup variables, only hypertension status showed a significant interaction with cumulative average LCI-WC in relation to incident cardiovascular disease (P for interaction = 0.003). Because multiple subgroup analyses were conducted, this interaction finding was considered exploratory and hypothesis-generating. Therefore, the hypertension-stratified results should be interpreted cautiously rather than as confirmatory evidence of differential effects.Higher cumulative average LCI-WC was significantly associated with an increased risk of incident cardiovascular disease among participants without

hypertension, whereas no statistically significant association was observed among those with hypertension.

Figure 6. Subgroup analyses of the association between cumulative average LCI-WC and incident cardiovascular disease. Forest plot showing adjusted odds ratios and 95% confidence intervals for the association between cumulative average LCI-WC and incident CVD across prespecified subgroups. The fully adjusted model included age, sex, education level, marital status, smoking status, alcohol consumption, eGFR, hypertension, diabetes, dyslipidemia, antihypertensive treatment, antidiabetic treatment, and lipid-lowering treatment, with the stratifying variable excluded from each subgroup-specific model. P values for interaction were obtained from likelihood ratio tests. CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; LCI-WC, lipoprotein combined index-waist circumference.

The fully adjusted model controlled for age, sex, education level, marital status, smoking, alcohol consumption, renal function (eGFR), hypertension, diabetes, dyslipidemia, antihypertensive treatment, antidiabetic treatment, and lipid-lowering treatment, with the stratifying variable excluded from each subgroup-specific model.

3.4 Sensitivity Analyses

In the complete-case sensitivity analysis, participants with missing data for any covariate were excluded, and the association between cumulative average LCI-WC and incident cardiovascular disease was re-evaluated using the fully adjusted model. The results were generally consistent with the main analysis. Compared with Q1, the ORs (95% CIs) were 1.260 (0.966–1.642) for Q2, 1.530 (1.182–1.980) for Q3, and 1.370 (1.051–1.786) for Q4. Each 1-SD increment in cumulative average LCI-WC was associated with a higher risk of incident cardiovascular disease (OR, 1.148; 95% CI, 1.049–1.257) (**Supplementary Table 3**).

After 1:1 propensity score matching, 1,868 matched pairs were generated between the Q1-Q2 and Q3-Q4 groups (**Supplementary Table 4**). The maximum absolute standardized mean difference (SMD) after matching was 0.0415, indicating good covariate balance. The association between cumulative average LCI-WC and incident CVD remained in the same direction and was statistically significant after matching (Q3-Q4 vs. Q1-Q2: OR, 1.31; 95% CI, 1.081–1.587; per 1-SD increment: OR, 1.155; 95% CI, 1.038–1.286) (**Supplementary Table 5**).

In the fully adjusted model, the original composite index without natural logarithmic transformation, WC x LCI, was further analyzed. WC x LCI showed an overall positive trend in association with incident CVD risk; however, the association was attenuated and was not consistently statistically significant after full adjustment. Compared with Q1, the ORs (95% CIs) were 1.120 (0.868–1.446) for Q2, 1.306 (1.018–1.676) for Q3, and 1.254 (0.973–1.615) for Q4. The OR per 1-SD increment was 1.085 (95% CI, 0.999–1.180) (**Supplementary Table 6**).

To further assess effect modification by hypertension status, an interaction term between LCI-WC and hypertension was added to the main model (**Supplementary Table 7**), and statistical significance was

evaluated using the likelihood ratio test. The results suggested that the positive association between cumulative average LCI-WC and incident cardiovascular disease was mainly present among participants without hypertension, whereas this association was not evident among participants with hypertension. These findings indicate that hypertension status may modify the association between cumulative average LCI-WC and incident cardiovascular disease.

Discussion

This prospective longitudinal study, based on a nationally representative cohort, included 4,597 Chinese middle-aged and older adults aged 45 years and above, with follow-up from 2011 to 2018. We found that LCI-WC, a composite indicator derived from natural log-transformed LCI and waist circumference, was significantly associated with the risk of incident cardiovascular disease (CVD). Participants with higher cumulative average LCI-WC had a greater risk of developing CVD, and this association remained significant after multivariable adjustment.

The cumulative average ln-transformed LCI-WC examined in this study may have several potential advantages over single lipid parameters or waist circumference alone. First, LCI-WC integrates two CVD-related metabolic dimensions: atherogenic lipid burden and central obesity. LCI incorporates TC, TG, LDL-C, and HDL-C, thereby capturing a broader pattern of atherogenic dyslipidemia than any single lipid parameter. By further combining LCI with waist circumference, LCI-WC also reflects central adiposity, which is closely related to cardiometabolic risk. Therefore, this composite indicator may provide a more comprehensive assessment of individuals with coexisting abdominal obesity and dyslipidemia. Second, the use of cumulative average LCI-WC from 2011 to 2015 may reduce random measurement error from a single assessment and better represent long-term metabolic exposure. In addition, incident CVD was assessed in 2018, which ensured a clear temporal sequence between exposure and outcome and reduced the likelihood of reverse causality. Third, LCI-WC may have broader applicability in CVD risk assessment. Previous studies of LCI have mainly focused on specific outcomes or populations, such as coronary heart disease, cardiorenal syndrome, or patients undergoing peritoneal dialysis [14][15]. In contrast, the present study evaluated incident CVD in a general middle-aged and older population, providing additional evidence for the potential utility of LCI-WC in population-based cardiovascular risk stratification.

After further classifying incident CVD into incident heart disease and incident stroke, we found that cumulative average LCI-WC was significantly associated with incident stroke, whereas its overall association with incident heart disease was not statistically significant. This finding appears to differ from previous studies[16]. One possible explanation is that heart disease in CHARLS was defined using a broad self-reported measure, which may include coronary heart disease, angina, heart failure, arrhythmia, and other cardiac conditions[17]. Such clinical heterogeneity may have diluted the association between LCI-WC and incident heart disease. In contrast, stroke may represent a more specific vascular outcome, suggesting that the association of LCI-WC may vary across different CVD subtypes. Biologically, LCI-WC may be more closely related to pathways involving atherosclerosis, endothelial dysfunction, chronic

inflammation, and cerebrovascular injury. However, the limited number of subtype-specific events may also have reduced statistical power, as there were 266 incident stroke cases and 415 incident heart disease cases, with some participants developing both outcomes.

In the subgroup analyses, the forest plot showed no significant interaction for most stratification factors, with all interaction P values greater than 0.05 except for hypertension. This finding suggests that the association between LCI-WC and incident CVD may be more evident among participants without hypertension. Among individuals with hypertension, CVD risk may be more strongly driven by blood pressure level, antihypertensive treatment, disease duration, and coexisting metabolic abnormalities[18], which could attenuate or obscure the independent association between LCI-WC and incident CVD.

We incorporated an interaction term between LCI-WC and hypertension into the primary model and performed a likelihood ratio test. The results indicated that hypertension status significantly modified the association between cumulative average LCI-WC and incident cardiovascular disease (CVD). Several plausible explanations may account for this finding. First, among individuals without hypertension, LCI-WC may serve as an early indicator of metabolic risk. Second, patients with hypertension already have an elevated baseline risk of CVD[19], which may attenuate the association between LCI-WC and incident CVD. Third, hypertension may lie on the mediating pathway linking abnormal lipid metabolism to CVD[20], although this hypothesis requires further validation in future studies. However, this subgroup finding should be interpreted with caution. The interaction analysis was exploratory, and multiple subgroup comparisons increase the possibility of chance findings. Therefore, the observed heterogeneity by hypertension status requires confirmation in independent cohorts before firm conclusions can be drawn.

After excluding participants with missing values for any covariates in the fully adjusted model, the association between the exposure and outcome remained statistically significant, suggesting that our findings were relatively robust to the handling of missing data. Nevertheless, multiple imputation relies on the missing at random (MAR) assumption; therefore, potential bias due to missing not at random (MNAR) mechanisms cannot be entirely ruled out. In addition, in the sensitivity analysis, the association between the untransformed composite indicator WC × LCI and incident CVD was weaker than that observed for WC × ln(LCI) in the primary analysis, although the overall risk trend remained positive. This pattern may be partly attributable to the pronounced skewness and extreme values of LCI, which is a product- and ratio-based lipid indicator. Natural log-transformation of LCI may reduce the disproportionate influence of extreme values, smooth the exposure distribution, and make the variable more suitable for inclusion in logistic regression models. The comparison of results further suggests that the composite indicator derived from log-transformed LCI may provide more stable cardiovascular risk stratification.

Because CHARLS is a nationally representative cohort of middle-aged and older Chinese adults, the findings may be most applicable to community-dwelling Chinese adults aged 45 years and older. However, extrapolation to younger populations, non-Chinese populations, or clinical populations should be made with caution.

Although this study used multiple statistical approaches and yielded relatively consistent findings, several limitations should be acknowledged. First, biomarker data in CHARLS were available only in 2011 and 2015; therefore, cumulative average LCI-WC could only be calculated based on these two waves. This limited our ability to characterize more detailed temporal trajectories of the exposure. Second, incident CVD was mainly defined according to self-reported physician-diagnosed heart disease or stroke, or the use of disease-specific treatment. The absence of further confirmation using medical imaging, laboratory examinations, or adjudicated clinical records may have introduced outcome misclassification. Third, LCI-WC is a novel composite indicator derived from previously established lipid-related indices, and evidence from high-quality independent cohorts remains limited. Therefore, our findings should be interpreted as exploratory and require further validation, particularly through comparisons of predictive performance and incremental value. In addition, although hypertension status showed a statistically significant interaction with LCI-WC, the subgroup analyses were exploratory and were not adjusted for multiple comparisons. Therefore, this finding may be susceptible to chance and should be validated in future studies.

Future studies should incorporate hospital-based real-world medical records and other large-scale public cohorts to externally validate the association between LCI-WC and incident CVD, and to assess its reproducibility across different populations. In addition, clinical risk prediction models incorporating LCI-WC could be developed and compared with existing lipid-related composite indicators, such as the atherogenic index of plasma (AIP)[21], in terms of discrimination, calibration, and clinical net benefit. Such analyses would help clarify whether LCI-WC provides incremental predictive value beyond established risk factors and related metabolic indices. With larger sample sizes, more complete follow-up information, and validated clinical outcomes, machine learning approaches may also be explored in future CVD risk prediction studies, thereby facilitating the translation of LCI-WC from an epidemiological association marker to a potential tool for cardiovascular risk stratification and early intervention.

Conclusions

Based on this CHARLS study, we found that cumulative average LCI-WC was significantly associated with incident cardiovascular disease among Chinese middle-aged and older adults. Exploratory subgroup analyses suggested that the association between cumulative average LCI-WC and incident CVD may differ by hypertension status, with a stronger association observed among participants without hypertension. However, this finding should be interpreted cautiously and requires external validation.These findings suggest that LCI-WC may have potential utility as a comprehensive indicator for cardiovascular risk stratification in middle-aged and older adults, and may help inform more individualized prevention and intervention strategies.

Abbreviations

CVD	Cardiovascular disease
CHARLS	China Health and Retirement Longitudinal Study
LCI	Lipoprotein combined index
LCI-WC	Lipoprotein combined index-waist circumference composite index
WC	Waist circumference
TC	Total cholesterol
TG	Triglycerides
LDL-C	Low-density lipoprotein cholesterol
HDL-C	High-density lipoprotein cholesterol
FBG	Fasting blood glucose
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
eGFR	Estimated glomerular filtration rate
BMI	Body mass index
TyG	Triglyceride-glucose index
TyG-BMI	Triglyceride-glucose-body mass index
LAP	Lipid accumulation product
VAI	Visceral adiposity index
AIP	Atherogenic index of plasma
RCS	Restricted cubic spline
OR	Odds ratio
CI	Confidence interval
SD	Standard deviation
SMD	Standardized mean difference
VIF	Variance inflation factor
PSM	Propensity score matching
LRT	Likelihood ratio test
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
Q1	Quartile 1

Q2	Quartile 2
Q3	Quartile 3
Q4	Quartile 4

Declarations

Acknowledgments

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Data Availability

The datasets generated and/or analysed during the current study are available in the China Health and Retirement Longitudinal Study repository [http://charls.pku.edu.cn].

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Competing Interests

We have no competing interests.

Author Contributions

Zhuoka Luo was responsible for the conception and design of the study. Xiaoqing Lang extracted and organized the data. Jie Zhou performed the statistical analyses, interpreted the results, drafted the manuscript, and conducted the literature search. All authors reviewed and approved the submitted version of the manuscript.

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Ethics approval and consent

The CHARLS study was conducted in accordance with the Declaration of Helsinki and was approved by the Biomedical Ethics Review Committee of Peking University (IRB00001052-11015). Ethical approval for biomarker collection was granted under IRB00001052-11014. All participants provided written informed consent. This secondary analysis used de-identified CHARLS data, and the authors did not have access to information that could identify individual participants.

During the fieldwork, each respondent who agreed to participate in the survey was asked to sign two copies of the informed consent, and one copy was kept in the CHARLS office, which was also scanned and saved in PDF format. Four separate consents were obtained: one for the main fieldwork, one for the non-blood biomarkers and one for the taking of the blood samples, and another for storage of blood for future analyses.

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Figures

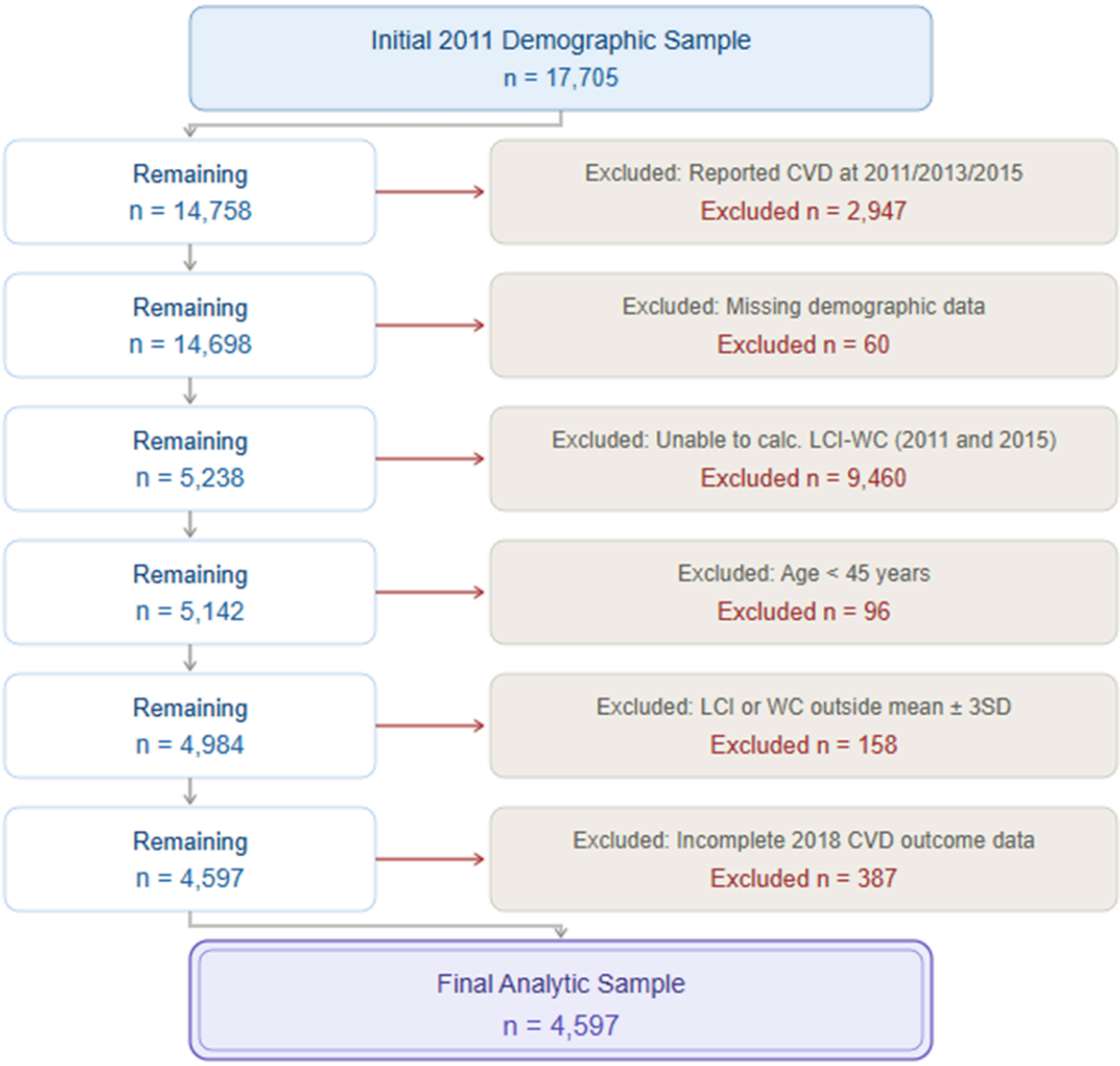


Figure 1

Flowchart of participant enrollment and follow-up. The flowchart shows the selection process of eligible participants from the CHARLS cohort. Participants with reported CVD during the 2011-2015 exposure assessment period, missing required exposure measurements, age <45 years, extreme LCI or WC values, or incomplete 2018 CVD outcome data were excluded. CVD, cardiovascular disease; LCI-WC, lipoprotein combined index-waist circumference.

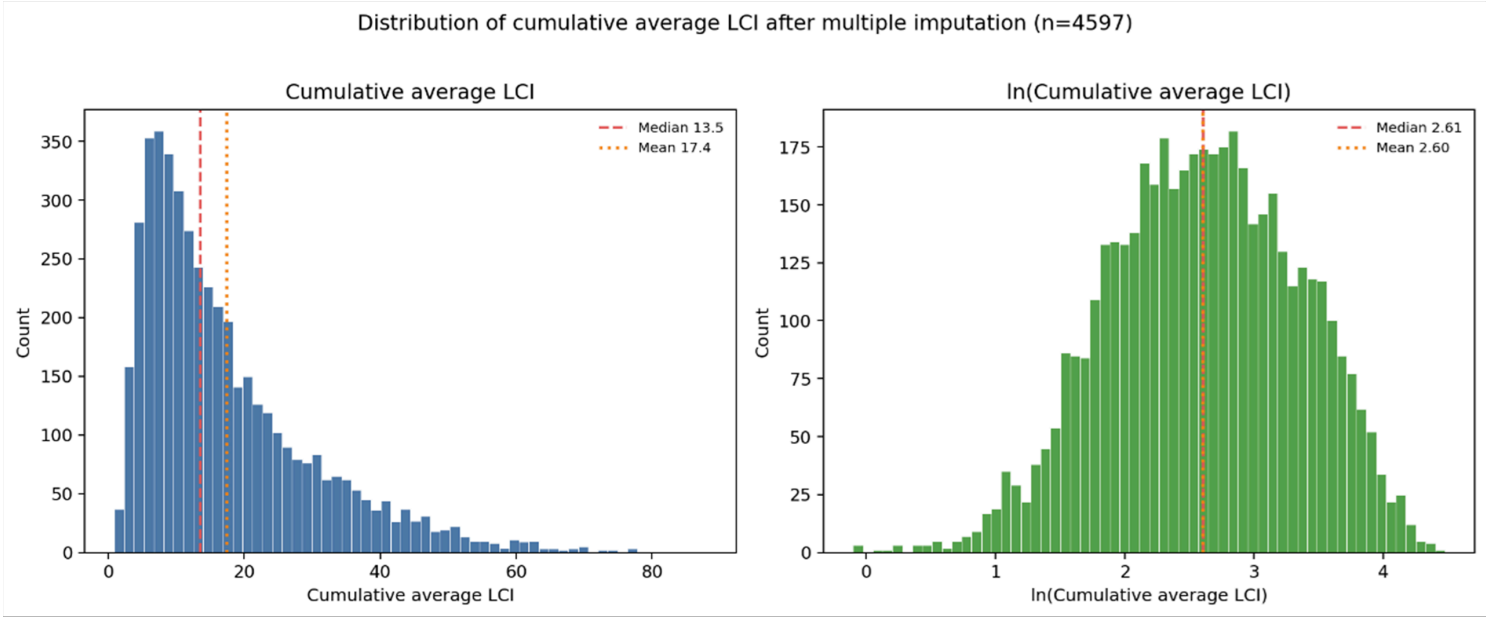


Figure 2

Distribution of cumulative average LCI after multiple imputation(n=4597). The histogram and box plot show the distribution of cumulative average LCI-WC among 4,597 participants. The dashed vertical lines indicate the mean and median values. LCI-WC, lipoprotein combined index-waist circumference.

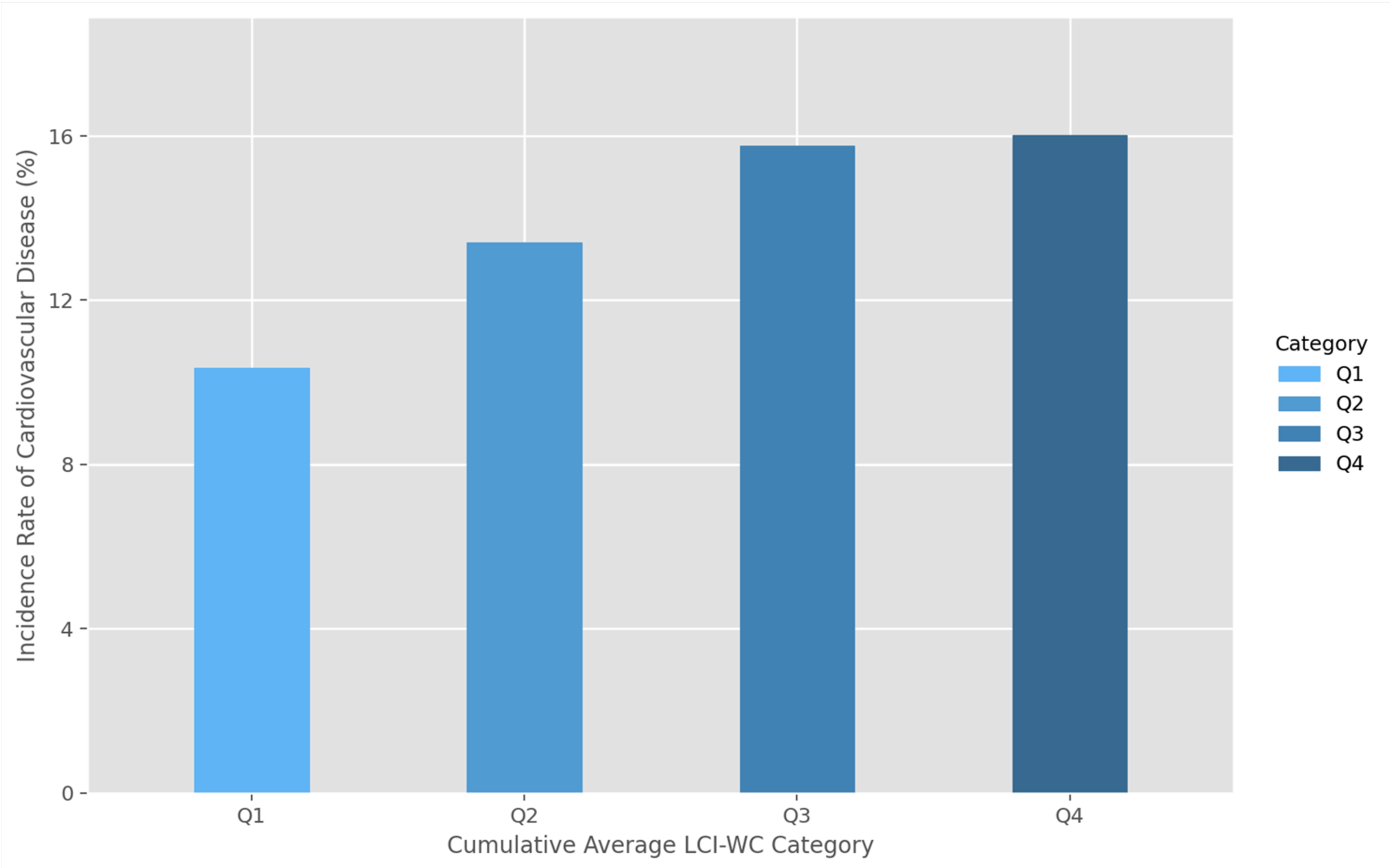


Figure 3

Incidence of cardiovascular disease by quartile of cumulative average LCI-WC (Q1–Q4). Bars show the proportion of participants with incident CVD in 2018 across quartiles of cumulative average LCI-WC. Q1-Q4 indicate increasing quartiles of cumulative average LCI-WC. CVD, cardiovascular disease; LCI-WC, lipoprotein combined index-waist circumference.

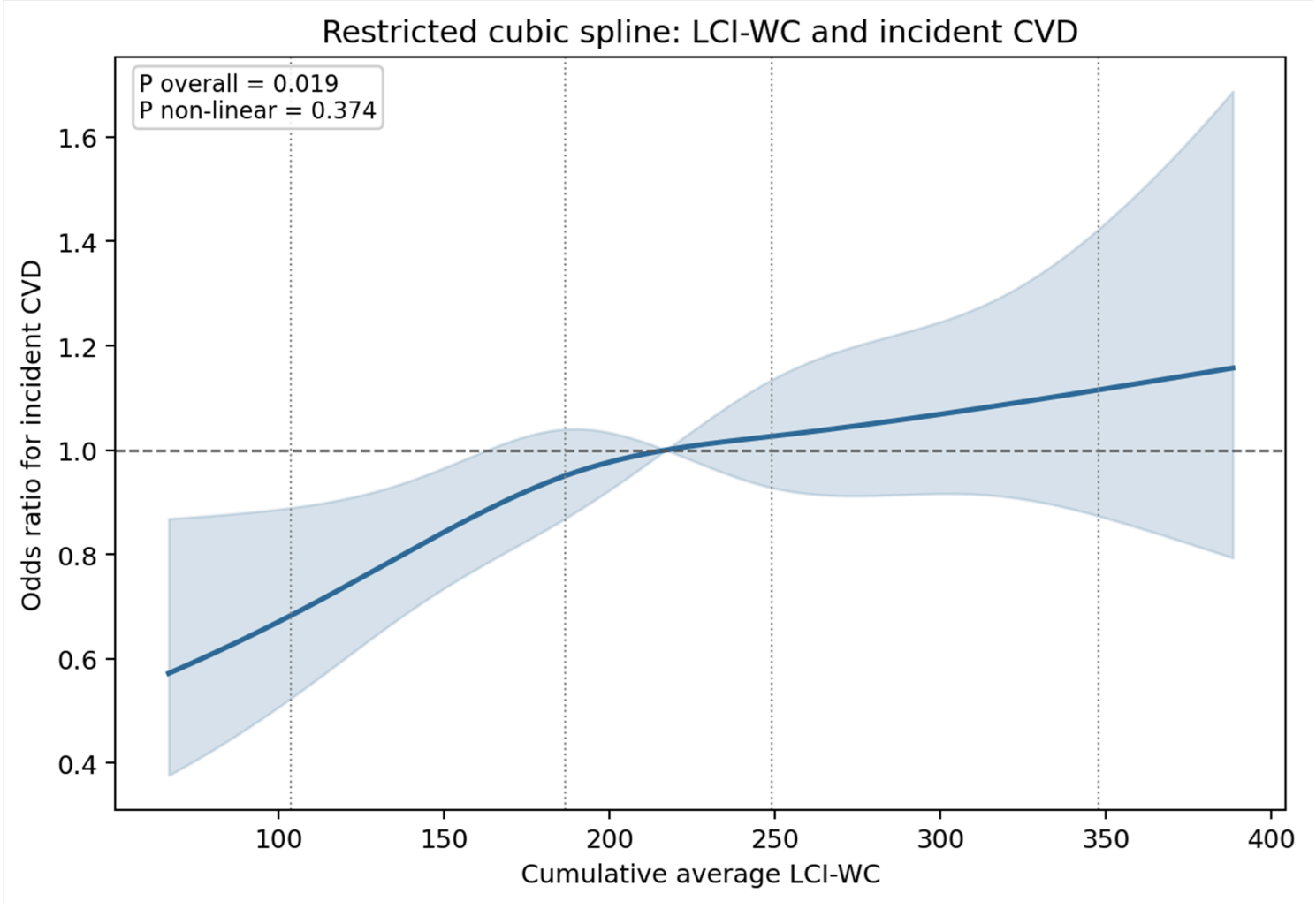


Figure 4

Association between cumulative average LCI-WC and incident cardiovascular disease. Restricted cubic spline analysis was used to evaluate the association between cumulative average LCI-WC and incident CVD. The solid line represents the adjusted odds ratio, and the shaded area represents the 95% confidence interval. The model was adjusted for age, sex, education level, marital status, smoking status, alcohol consumption, eGFR, hypertension, diabetes, dyslipidemia, antihypertensive treatment, antidiabetic treatment, and lipid-lowering treatment. CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; LCI-WC, lipoprotein combined index-waist circumference

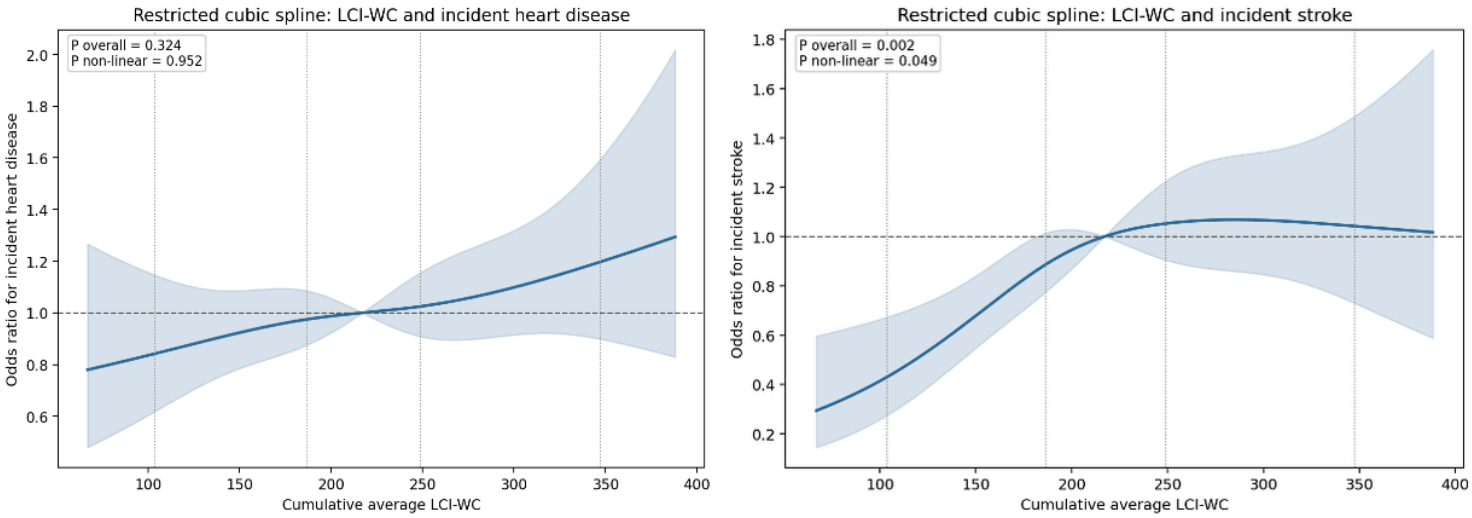


Figure 5

Association between cumulative average LCI-WC and incident heart disease (left) and incident stroke (right). Restricted cubic spline analyses were used to evaluate the associations of cumulative average LCI-WC with incident heart disease and incident stroke. The solid lines represent adjusted odds ratios, and the shaded areas represent 95% confidence intervals. Models were adjusted for age, sex, education level, marital status, smoking status, alcohol consumption, eGFR, hypertension, diabetes, dyslipidemia, antihypertensive treatment, antidiabetic treatment, and lipid-lowering treatment. eGFR, estimated glomerular filtration rate; LCI-WC, lipoprotein combined index-waist circumference.

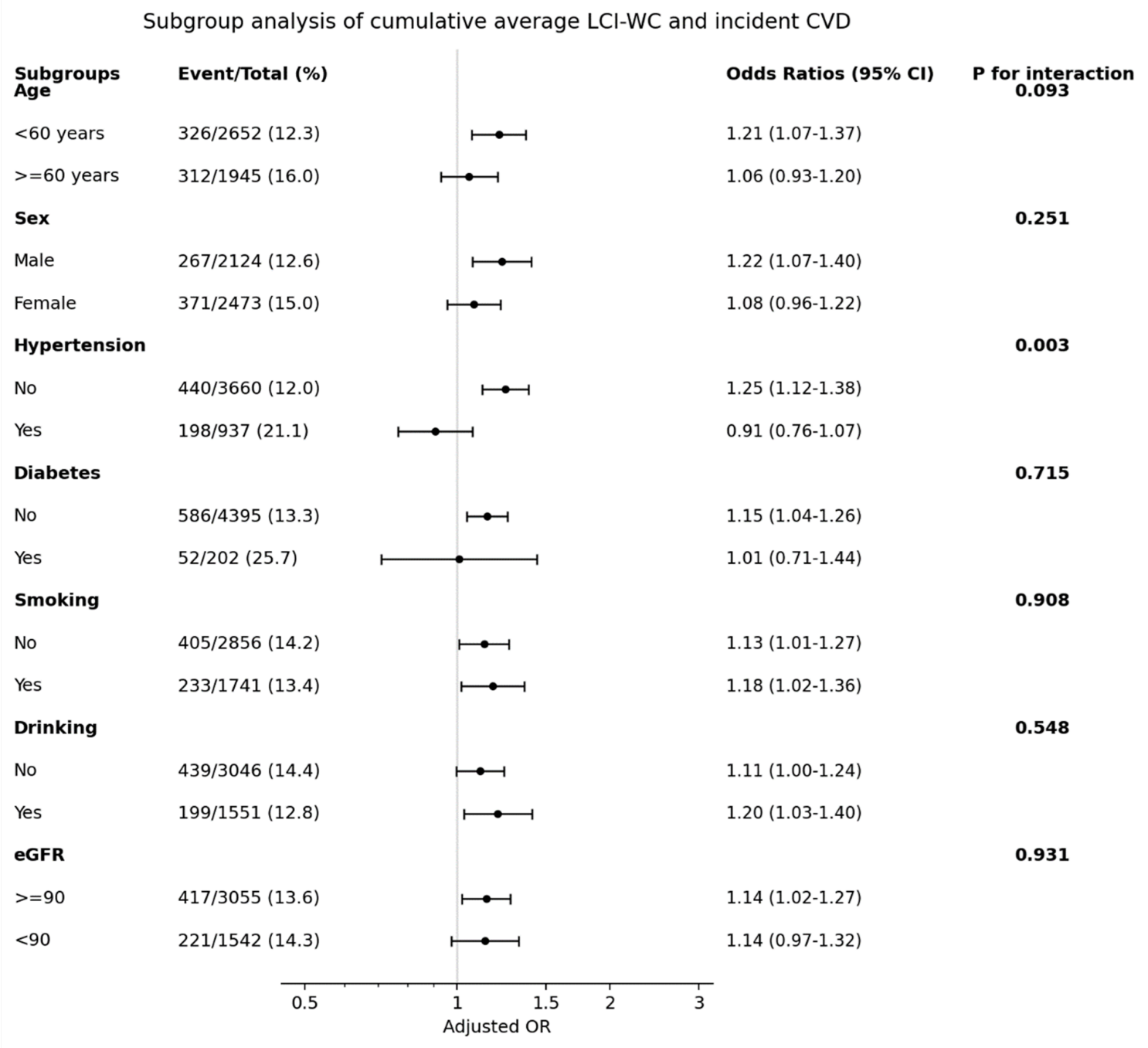


Figure 6

Subgroup analyses of the association between cumulative average LCI-WC and incident cardiovascular disease. Forest plot showing adjusted odds ratios and 95% confidence intervals for the association between cumulative average LCI-WC and incident CVD across prespecified subgroups. The fully adjusted model included age, sex, education level, marital status, smoking status, alcohol consumption, eGFR, hypertension, diabetes, dyslipidemia, antihypertensive treatment, antidiabetic treatment, and lipid-lowering treatment, with the stratifying variable excluded from each subgroup-specific model. P values for interaction were obtained from likelihood ratio tests. CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; LCI-WC, lipoprotein combined index-waist circumference.

Supplementary Files

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