Research Square

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Longitudinal estimated glucose disposal rate trajectories and cumulative exposure predict cardiovascular disease in population with Cardiovascular- Kidney-Metabolic syndrome stages 0-3: A nationwide prospective cohort study

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Abstract

Background

The baseline estimated glucose disposal rate (eGDR), a surrogate for insulin resistance (IR), is linked to cardiovascular disease (CVD) in early-stage Cardiovascular-Kidney-Metabolic (CKM) syndrome. However, the impact of its longitudinal changes is unknown. We aimed to explore the dynamic changes in eGDR—cumulative exposure and control level trajectories—are associated with CVD incidence in individuals with CKM syndrome stages 0–3.

Methods

In this nationwide prospective cohort study, we analyzed data from 4,667 participants in the China Health and Retirement Longitudinal Study (CHARLS) without baseline CVD. We assessed dynamic changes in eGDR between 2012 and 2015 using two metrics: cumulative eGDR (cum eGDR), reflecting total burden over three years, and eGDR control levels (eGDR trajectories), derived from K-means clustering to identify the longitudinal trajectories (Persistent High, Rapidly Decreas- ing, and Persistent Low group). The primary outcome was incident CVD events during follow-up to 2018.

Results

A total of 4667 CKM syndrome stages 0–3 participants were included in the study, of whom 571 developed CVD during the 3-year follow-up period. Multivariate Logistic regression analysis showed that Class 2 (OR = 1.312, 95% CI: 1.042–1.652; P = 0.021) and Class3 (OR = 2.228, 95% CI: 1.728–2.872; P = 0.001) had significantly higher risk of CVD compared with Class 1 at the eGDR trajectories. In addition, the elevated cum eGDR (OR = 0.581, 95% CI: 0.515–0.656; P = 0.001) was associated with the decrease of the risk in CVD. Subsequent subgroup analyses revealed that eGDR trajectories were influenced by T2 diabetes mellitus (DM) status (P = 0.007), whereas cum eGDR remained unaffected (P > 0.05). Further, mediation analyses in the non-DM population showed that the effect of eGDR trajectories on new-onset CVD was partially mediated by lipid factors.

Conclusions

Our study demonstrates that worsening longitudinal eGDR trajectories and greater cum eGDR are powerful predictors of CVD in population with CKM syndrome stages 0–3. The association between eGDR trajectories and CVD was particularly significant in the non-DM population and was partially mediated by lipid factors. These highlight the ability of dynamic eGDR surveillance to guide early targeted prevention strategies.

Introduction

The American Heart Association (AHA) recently introduced the concept of Cardiovascular-Kidney-Metabolic (CKM) syndrome, a systemic disorder defined by the pathophysiological interplay between metabolic risk

factors, chronic kidney disease (CKD), and the cardiovascular system.[1–4] CKM syndrome affects almost all major organ systems and can cause serious clinical complications, including the nervous system,[5] digestive system,[6] and respiratory system.[7] However, numerous studies have shown that the clinical burden of CKM syndrome is primarily driven by cardiovascular disease (CVD).[1, 3, 8, 9] Due to the absence of conspicuous symptoms in the initial stages of CKM syndrome, and the emphasis of AHA on early screening for patients in stages 0–3, it is crucial to identify and intervene promptly in high-risk CVD patients within CKM syndrome stages 0–3.[1, 10]

Insulin resistance (IR), as a critical marker of metabolic dysfunction, plays an important role in the development of CKM syndrome.[1] The gold standard for IR evaluation is the hyperinsulemic euglycemic clamp (HEC),[11] but the complexity of HEC operation limits its clinical application.[12] In this regard, an established and useful surrogate marker for measuring IR is the estimated glucose disposal rate (eGDR).[13] The eGDR is calculated from clinical parameters such as waist circumference (WC), hypertension status and glycosylated hemoglobin A1c (HbA1c), providing a novel noninvasive measure of insulin sensitivity.[13] It is closely related to metabolic and cardiovascular risk.[14, 15] When compared with other measures of IR, it has a higher predictive value for the incidence of CVD in both the general population and the population with CKM syndrome stages 0–3.[16–18] However, existing studies have predominantly relied on single, static measurements of eGDR, which may not fully capture the risk associated with long-term metabolic dysregulation and its temporal variability. Assessing the long-term burden and trajectory of eGDR may therefore offer a more comprehensive and accurate evaluation of cardiovascular risk. Therefore, this study takes a large, nationwide prospective cohort to investigate the association of dynamic changes in eGDR, quantified by both cumulative exposure and distinct temporal trajectories, with the incidence of CVD among individuals with CKM syndrome stages 0–3.

Method

Study population

The China Health and Retirement Longitudinal Study (CHARLS), which is run by the Chinese Academy of Social Sciences, Peking University's National School, is a nationally representative study that focuses on middle-aged and older people (45 years of age and over). Previous publication have provided more information about the research population.[19] Study eligibility criteria included no history of cancer, no history of CVD (including stroke) before 2015, complete data on fasting blood glucose (FBG), glycosylated hemoglobin (GHB) and waist circumference (WC) are available and completed information of CKM syndrome stages 0–3. CHARLS was approved by Peking University Institutional Review Board (IRB 00001052–11015) and all participants provided written informed consent prior to enrollment in the study. Participants interviewed from 2011–2012 were used as a baseline (Wave 1), and follow-up was conducted in 2013 (Wave 2), 2015 (Wave 3) and 2018 (Wave 4).

The exclusion criteria for participants are shown in Fig. 1. Finally, a total of 4667 participants were included in the analysis.

Data collection and definitions

Various covariates were assessed based on the CHARLS questionnaire and dataset, including basic demographic characteristics (gender, age, education, marriage, place of residence, etc.), lifestyle factors

(smoking and alcohol use status), comorbidities (hypertension, T2DM and CVD), simple physical measurements [systolic blood pressure, diastolic blood pressure, height, weight, body mass index (BMI), WC], and blood biomarkers.[19]

The definition of CKM syndrome stages 0–3: Stage 0 includes individuals without CKM syndrome risk factors; Stage 1: involves overweight, abdominal obesity, or adipose tissue dysfunction without CKD; Stage 2: includes individuals with metabolic risk factors (such as dyslipidemia, hypertension, metabolic syndrome, or type 2 diabetes), moderate to high risk CKD, or both; Stage 3: includes individuals at high risk or with subclinical CVD.[1, 20]

The eGDR (mg/kg/min) was calculated as previously described according to the following formula: eGDR = 21.158-(0.09 * WC) -(3.407 * HT) -(0.551* HbA1c) [WC = waist circumference (cm), HT = hypertension (yes = 1/no = 0), and HbA1c = HbA1c (%)].[21] Then, the Cumulative eGDR (cum eGDR), as an area-under-the-curve estimate (mean TyG*time span), was calculated as $(eGDR_{2012}+eGDR_{2015})/2* time_{(2015-2012)}$.[22, 23] Meanwhile, the cum eGDR was divided into groups by tertiles (Q3:high group; Q2: middle group and Q1: low group). Subsequently, the participants were divided into three eGDR trajectory groups based on eGDR trajectories using K-means analysis[22]: Class 1: Persistent High Group; Class 2: Rapidly Decreasing Group and Class 3: Persistent Low Group.

Model 1: Unadjusted + Age+Gender.

Model 2: Model1 + T2DM+Dyslipidemia+Currently smoking+Alcoholic + BMI+ Education+Household Register

Outcomes

The primary endpoint of the study was the incidence of CVD (including stroke).

In follow-up period (wave 4), participants who had answered “yes” to the question of “Have you been diagnosed by your doctor with [heart attack, coronary heart disease, angina, congestive heart failure, or other cardiac problems]? ” or “Have you been diagnosed with stroke by a doctor?” were considered as occurring CVD events according to the previous studies.[24, 25]

Statistical analysis

All the data were analyzed with R4.3.0. Normally distributed continuous variables are expressed as the mean ± standard deviation (SD), while non-normally distributed variables were expressed as median (interquartile range, IQR). The differences among groups were determined by Student’s t test, the Wilcoxon rank sum test or one-way analysis of variance (ANOVA). Categorical variables were compared via the chi-square test or Fisher’s exact test.

The participants were divided into three eGDR trajectories groups according to the K-means clustering analysis. K-means clustering is a technique for dividing N observations into K clusters.[26] It can effectively capture subtle changes in the dynamic changes of eGDR and provide scientific evidence for revealing its relationship with CVD risk. The study used Elbow rule and Gap Statistic to determine the optimal number of clusters is three. (Fig. 2A, B) As shown in Fig. 2C, each observation is assigned to the cluster with the closest mean value, which serves as the prototype of the cluster. Subsequently, the study employed logistic regression analysis to evaluate

the association between dynamic changes in eGDR and the incidence of CVD, utilizing eGDR trajectories, continuous cum eGDR, and cum eGDR tertiles. Additionally, restricted cubic spline (RCS) was employed to explore potential linear relationships between cum eGDR and stroke incidence in participants with CKM syndrome. Subgroup analysis was used to explore heterogeneity among different subpopulations. To explore potential mechanisms underlying the association between dynamic changes in eGDR and new-onset CVD, mediation analysis was performed. For robustness of the results, a comprehensive sensitivity analysis was performed. A two-sided P value of < 0.05 was considered to represent statistical significance.

Results

Baseline characteristics

As shown in Table 1, it summarizes the baseline characteristics of participants with CKM syndrome stages 0–3, categorized into three groups based on eGDR trajectories (Class 1–3 groups): (1) Class 1 (N = 2205): Persistent High Group; (2) Class 2 (N = 1516): Rapidly Decreasing Group; (3) Class 3 (N = 946): Persistent Low Group. Overall, significant differences were observed among these three groups in terms of age, gender, adverse lifestyle factors (smoking or alcohol consumption), comorbidities (hypertension, T2DM, or dyslipidemia), biochemical markers, and CKM syndrome stage. Specifically, Class 3 represents the group with the poorest eGDR trajectories. Compared to the other groups, it exhibited higher BMI and WC, a greater proportion of comorbidities, and more pronounced abnormalities in biochemical markers (hs-CRP, HbA1c, or eGFR).

Table 1
Characteristics of the study participants.

	[ALL]	Class 1	Class 2	Class 3	p.overall
	N = 4667	N = 2205	N = 1516	N = 946	
Basic data					
AGE ≥ 60	1817 (38.933%)	796 (36.100%)	571 (37.665%)	450 (47.569%)	0.001
Female	2547 (54.575%)	1143 (51.837%)	836 (55.145%)	568 (60.042%)	0.001
Household Register					0.001
Agricultural	4083 (87.543%)	1987 (90.113%)	1289 (85.139%)	807 (85.397%)	
Non-Agricultural	581 (12.457%)	218 (9.887%)	225 (14.861%)	138 (14.603%)	
Education					0.421
Lower than high school	3281 (70.302%)	1560 (70.748%)	1047 (69.063%)	674 (71.247%)	
High school or above	1386 (29.698%)	645 (29.252%)	469 (30.937%)	272 (28.753%)	
Height	157.986 (8.422)	157.572 (8.194)	158.520 (8.415)	158.095 (8.901)	0.003
Weight	58.787 (11.088)	53.694 (8.780)	62.267 (10.213)	65.080 (11.852)	0.001
BMI	23.505 (3.828)	21.593 (2.945)	24.716 (3.192)	26.020 (4.310)	0.001
Waist	83.982 (12.179)	77.302 (10.756)	88.557 (10.369)	92.221 (9.194)	0.001
Cardiovascular data					
SBP	128.525 (20.450)	121.062 (16.707)	129.937 (19.677)	143.658 (20.756)	0.001
DBP	75.140 (11.775)	71.308 (10.459)	76.119 (11.118)	82.502 (11.883)	0.001
HR	72.000 (10.021)	71.220 (9.808)	72.477 (10.015)	73.052 (10.384)	0.001
Behavior					
Currently smoking	1759 (37.731%)	892 (40.545%)	557 (36.741%)	310 (32.770%)	0.001
Alcoholic	1598 (34.277%)	817 (37.136%)	514 (33.905%)	267 (28.224%)	0.001

Abbreviation: DM: Diabetes mellitus, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR:Heart rate, TG: triglyceride, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, SCr: serum creatine, UA: Uric acid, WBC: white blood cell, HGB: hemoglobin, GLU: glucose, GHB: glycated hemoglobin, WBC: White blood cell, TC: Total cholesterol, BUN: Blood Urea Nitrogen, eGFR: Estimated glomerular filtration rate, eGDR: Estimated Glucose Disposal Rate, CKM syndrome: Cardiovascular-kidney-metabolic syndrome

	[ALL]	Class 1	Class 2	Class 3	p.overall
	N = 4667	N = 2205	N = 1516	N = 946	
Basic data					
Past medical history					
Hypertension	895 (19.177%)	2 (0.091%)	87 (5.739%)	806 (85.201%)	0.001
Dyslipidemia	317 (6.792%)	61 (2.766%)	90 (5.937%)	166 (17.548%)	0.001
DM	730 (15.642%)	185 (8.390%)	278 (18.338%)	267 (28.224%)	0.001
Laboratory data					
WBC	6.193 (1.858)	6.103 (1.841)	6.206 (1.822)	6.382 (1.941)	0.001
Platelets	211.741 (77.662)	209.579 (73.459)	214.044 (73.029)	213.090 (92.865)	0.190
BUN	15.615 (4.320)	15.666 (4.291)	15.557 (4.342)	15.591 (4.355)	0.901
GLU	102.240 [94.320;112.320]	99.720 [92.340;108.000]	103.320 [95.760;115.380]	105.660 [97.785;121.815]	0.001
Scr	0.762 (0.177)	0.752 (0.167)	0.768 (0.179)	0.774 (0.197)	0.002
TC	192.815 (38.309)	187.922 (36.029)	195.825 (38.169)	199.397 (42.064)	0.001
TG	104.430 [73.898;153.105]	92.040 [66.375;129.210]	114.165 [80.535;175.230]	127.440 [88.500;188.505]	0.001
HDL-C	51.186 (15.218)	54.904 (15.280)	48.481 (14.402)	46.853 (14.270)	0.001
LDL-C	115.341 (34.421)	111.836 (32.267)	118.431 (35.212)	118.557 (37.146)	0.001
Hs-CRP	0.950 [0.520;1.950]	0.760 [0.450;1.540]	1.080 [0.590;2.080]	1.340 [0.702;2.600]	0.001
GHB	5.100 [4.900;5.400]	5.100 [4.800;5.300]	5.200 [4.900;5.500]	5.300 [4.900;5.600]	0.001
UA	4.346 (1.203)	4.180 (1.128)	4.452 (1.258)	4.562 (1.229)	0.001
HB	14.200 [13.000;15.400]	14.000 [12.800;15.200]	14.300 [13.100;15.600]	14.400 [13.200;15.675]	0.001
eGFR	100.637 [91.395;106.972]	101.899 [92.820;107.765]	100.260 [91.503;106.846]	98.534 [87.522;104.678]	0.001

Abbreviation: DM: Diabetes mellitus, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR:Heart rate, TG: triglyceride, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, SCr: serum creatine, UA: Uric acid, WBC: white blood cell, HGB: hemoglobin, GLU: glucose, GHB: glycated hemoglobin, WBC: White blood cell, TC: Total cholesterol, BUN: Blood Urea Nitrogen, eGFR: Estimated glomerular filtration rate, eGDR: Estimated Glucose Disposal Rate, CKM syndrome: Cardiovascular-kidney-metabolic syndrome

	[ALL]	Class 1	Class 2	Class 3	p.overall
	N = 4667	N = 2205	N = 1516	N = 946	
Basic data					
Cumulative eGDR	28.975 (5.915)	33.645 (2.203)	28.207 (2.080)	19.317 (3.044)	0.001
$eGDR_{2012}$	10.061 (1.988)	11.411 (0.993)	10.078 (0.915)	6.887 (1.236)	0.001
$eGDR_{2015}$	9.255 (2.271)	11.019 (1.118)	8.727 (1.298)	5.991 (1.219)	0.001
CKM syndrome stages					0.001
0–1	2486 (53.268%)	1573 (71.338%)	866 (57.124%)	47 (4.968%)	
2	1340 (28.712%)	199 (9.025%)	340 (22.427%)	801 (84.673%)	
3	841 (18.020%)	433 (19.637%)	310 (20.449%)	98 (10.359%)	
Outcome					
The incidence of CVD	571 (12.235%)	197 (8.934%)	178 (11.741%)	196 (20.719%)	0.001

Abbreviation: DM: Diabetes mellitus, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR:Heart rate, TG: triglyceride, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, SCr: serum creatine, UA: Uric acid, WBC: white blood cell, HGB: hemoglobin, GLU: glucose, GHB: glycated hemoglobin, WBC: White blood cell, TC: Total cholesterol, BUN: Blood Urea Nitrogen, eGFR: Estimated glomerular filtration rate, eGDR: Estimated Glucose Disposal Rate, CKM syndrome: Cardiovascular-kidney-metabolic syndrome

Association of dynamic change in eGDR with CVD incidence in population with CKM syndrome stages 0–3.

In multivariable-adjusted logistic regression models, both longitudinal metrics of eGDR were significantly associated with incident CVD (Table 2). Compared with the Persistent High group (Class 1), individuals in the Rapidly Decreasing group (Class 2; OR: 1.312, 95% CI: 1.042–1.652, P = 0.021) and the Persistent Low group (Class 3; OR: 2.228, 95% CI: 1.728–2.872, P = 0.001) faced a significantly elevated risk of CVD. Similarly, a higher cumulative eGDR was associated with a lower risk of CVD, both when analyzed as a continuous variable (per SD increase, OR: 0.691, 95% CI: 0.624–0.766, P = 0.001) and by tertiles. Compared to the highest tertile (Q3), the middle (Q2; OR: 1.317, 95% CI: 1.019–1.706, P = 0.036) and lowest (Q1; OR: 2.289, 95% CI: 1.767–2.978, P = 0.001) tertiles of cumulative eGDR were associated with progressively higher CVD risk. Further, RCS curves displays a linear association between cum eGDR and the risk of CVD. (**Supplementary Fig. 1**)

Table 2
Logistic regression results for the association of eGDR trajectories and cumulative eGDR with new-onset CVD among individuals with CKM syndrome stages 0–3.

Group	Unadjusted		Model1		Model2	
	OR	P_value	OR	P_value	OR	P_value
eGDR control levels						
Class 1	REF	REF	REF	REF	REF	REF
Class 2	1.356(1.094–1.680)	0.005	1.341(1.081–1.662)	0.008	1.312(1.042–1.652)	0.021
Class 3	2.664(2.149–3.303)	0.001	2.519(2.028–3.129)	0.001	2.228(1.728–2.872)	0.001
Cumulative eGDR						
Per SD	0.666(0.614–0.723)	0.001	0.678(0.625–0.737)	0.001	0.691(0.624–0.766)	0.001
Tertiles of cumulative eGDR						
Q3	REF	REF	REF	REF	REF	REF
Q2	1.314(1.030–1.681)	0.028	1.316(1.031–1.684)	0.028	1.317(1.019–1.706)	0.036
Q1	2.543(2.040–3.187)	0.001	2.446(1.959–3.068)	0.001	2.289(1.767–2.978)	0.001
Model 1: Unadjusted + Age+Gender.						
Model 2: Model 1 + DM+Dyslipidemia+Currently smoking+Alcoholic + BMI+Education+ Household Register						

Subgroup analysis and exploration of underlying mechanisms

Subgroup analyses were performed to assess the consistency of these associations across different subpopulations (Fig. 3). The study population was stratified into subgroups based on age (≥ 60/<60 years), gender (male/female), education level (high school or above/less than high school), current smoking status (yes/no), alcohol consumption (yes/no), hypertension (yes/no), T2DM (yes/no), and dyslipidemia (yes/no). A significant interaction was observed between eGDR trajectories and T2DM (P for interaction = 0.007), suggesting that the predictive value of eGDR trajectories for CVD risk differs between individuals with and without T2DM. No significant interactions were found for cum eGDR in all tested subgroups (P for interaction > 0.05).

To further investigate the mechanism underlying this observed interaction, we conducted a mediation analysis stratified by T2DM. In the non-diabetic population, the association between adverse eGDR trajectories and incident CVD was partially mediated by lipid levels (Fig. 4). Specifically, total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) accounted for 4.99% and 4.39% of the total effect, respectively (both P < 0.05). In

contrast, no significant mediation by lipid factors was observed in the population with T2DM (**Supplementary Table 1**).

Sensitivity analyses conducted using various models demonstrated that eGDR trajectories and cum eGDR remained strongly associated with the incidence of CVD. (**Supplementary Table 2**)

Discussion

In this large, nationwide prospective cohort of individuals with CKM syndrome stages 0–3, we demonstrate that the dynamic changes in eGDR is a powerful predictor of future CVD risk. Our principal findings are threefold. Firstly, a greater cumulative burden of IR, lower cum eGDR, is strongly associated with higher CVD risk. Second, and more importantly, K-means cluster analysis of dynamic changes in eGDR identified different risk trajectories, with a pattern of rapid decrease in eGDR conferring a significant risk. These associations were robust after adjustment for a wide range of confounders. Crucially, we found that the predictive ability of eGDR trajectories was most pronounced in individuals without T2DM, an effect partially mediated by lipid factors.

The AHA recommends early intervention for CKM syndrome stage 0–3 patients, especially those at high risk for CVD.[1, 10] The IR marker can reflect the relationship between metabolic disorders and CVD, which makes a great contribution to this. In studies by Liao et al. and Zhang et al., eGDR was strongly associated with CVD in both T2DM and non-DM populations.[16, 27] Furthermore, in a general population study, eGDR was not only strongly associated with CVD but also demonstrated greater predictive value than other IR markers.[28] In a study comparing the predictive ability of different IR markers for CVD in populations with CKM syndrome stages 0–3, eGDR was identified as the most predictive marker.[29] These results highlight the importance of monitoring and managing eGDR in the early detection and intervention of CKM syndrome. However, given the inherent variability of single-point measurements, the dynamic changes in eGDR may more accurately reflect disease progression in individuals with CKM syndrome stages 0–3.

Cumulative exposure has become a widely used method for handling repeated measures data in longitudinal studies, reflecting the intensity and duration of exposure to a parameter over time.[30, 31] Our results showed that a lower cum eGDR was strongly associated with a higher risk of CVD in population with CKM syndrome stages 0–3. Similar to cumulative LDL-C,[32] cum eGDR can be used as a comprehensive marker of long-term metabolic damage sustained by vascular system. The components of the eGDR formula—waist circumference(WC), hypertension, and HbA1c—represent central obesity,[33] glycemic dysregulation,[34] and hemodynamic stress,[35] respectively. The cum eGDR effectively captures the aggregate burden of these core CKM syndrome risk components over time, explaining its strong and stable predictive performance across various subgroups in our analysis.

In addition to cumulative load, we employ K-means clustering, an unsupervised machine learning approach that provides deeper insights into patterns of metabolic deterioration.[22, 24] Our results identified three trajectories where eGDR changes over time. This result revealed a "Rapidly Decreasing" group, a high-risk phenotype that would be missed by conventional static assessments. Individuals in this group may not have the lowest absolute eGDR at any single point, but their accelerated rate of decline signifies a failure of metabolic homeostasis and portends a significantly increased risk of future CVD. This highlights the superior predictive value of tracking temporal patterns over relying on single-point measurements for risk stratification.

The most novel finding of our study is the significant interaction between eGDR trajectories and T2DM. The association between adverse eGDR trajectories and CVD was strong and clear in the non-DM population but was attenuated in individuals with T2DM. Our mediation analysis provides a possible mechanistic explanation for this observation. In the non-DM cohort, the link between worsening IR and CVD was partially mediated by rising levels of TC and LDL-C. This finding can be explained by a classical pathophysiological cascade: IR in fat and liver tissue drives dyslipidemia-characterized by increased VLDL production, decreased HDL levels, and the formation of small, dense LDL particles-which in turn promotes CVD.[36, 37]

In contrast, this situation is not significant in the population with T2DM. This suggests that once an individual progresses to overt T2DM, the landscape of CVD risk becomes substantially more complex.[38] In patients with T2DM, the overall CVD risk is driven by a potent confluence of multiple, powerful pathogenic mechanisms that go beyond IR-induced dyslipidemia. These include chronic hyperglycemia,[39] the formation of advanced glycation end-products (AGEs),[40] profound endothelial dysfunction,[41] renal impairment,[42] and systemic chronic inflammation.[43] These coexisting factors may collectively affect the overall risk, thereby weakening the predictive value of the eGDR trajectory. This finding suggests that the major drivers of CVD risk may shift as individuals progress in CKM syndrome.

In conclusion, our study shows that longitudinal trajectories and cumulative burden obtained by dynamic monitoring of eGDR are powerful and independent predictors of new-onset CVD in population with CKM syndrome stages 0–3. The differential role of lipid metabolism disorders as mediators in non-DM and T2DM populations provides new insights into the evolving pathophysiology of CKM syndrome. These findings strongly support dynamic eGDR surveillance as a practical and effective strategy to enhance CVD risk stratification and guide early preventive care.

Study strengths and limitations

Our study has several strengths, including its large, nationally representative cohort, prospective design, and the innovative use of two complementary methods to assess dynamic change in eGDR. However, there are some limitations to our study. First, the outcome are based on patient self-reports, which may introduce recall bias. Second, with only two time-points for eGDR measurement, our trajectory of eGDR is simplified. Third, although we adjusted for multiple confounders, we could not completely rule out residual confounders. Finally, the study population is middle-aged and elderly China population, and further validation may be required in more diverse populations.

Conclusion

Our study demonstrates that worsening longitudinal eGDR trajectories and greater cum eGDR are powerful predictors of CVD in population with CKM syndrome stages 0–3. The association between eGDR trajectories and CVD was particularly significant in the non-DM population and was partially mediated by lipid factors. These highlight the ability of dynamic eGDR surveillance to guide early targeted prevention strategies.

Declarations

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Conflict of interest statement

The authors declare that they have no competing interests.

Ethics declaration

CHARLS was approved by Peking University Institutional Review Board in accordance with the Declaration of Helsinki. (IRB 00001052 - 11015)

Human Ethics and Consent to Participate declarations

All participants provided written informed consent prior to enrollment in the study.

Authors' contribution

Yifei Xiang, Hongpeng Chen, Haitao Cao - concept and design, analyzed data, created tables and figures, drafted paper.

Anan Huang, Jie Wang - data cleansing.

Bingchen Liu - concept and design, supervised, edited paper.

Data availability statement

The data can be accessed via the following link：https://charls.pku.edu.cn/

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Figures

Figure 1 | The flow chart of study participants.

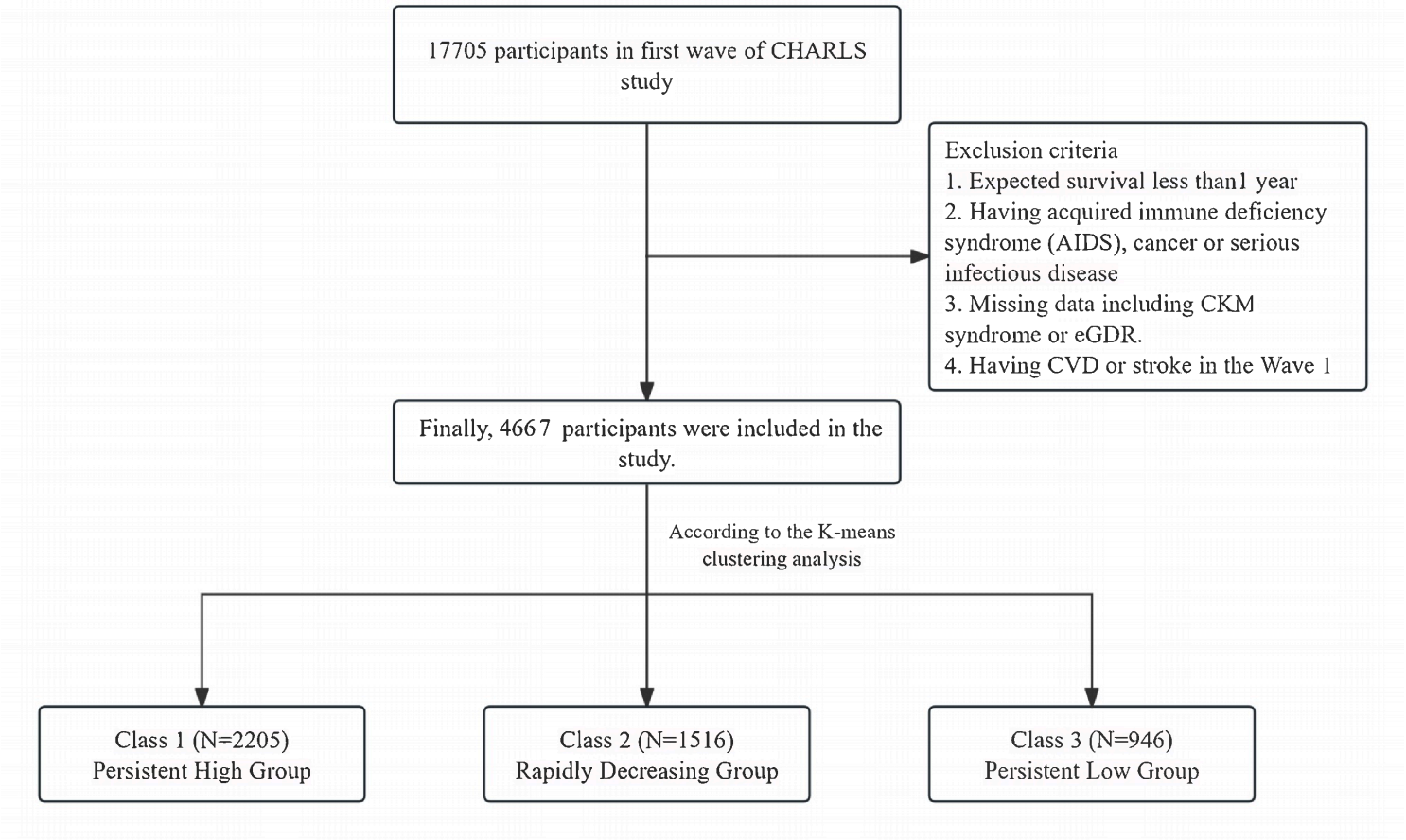


Figure 1

See image above for figure legend

Figure 2 | The clustering analysis results of K-means algorithm. (**A,B**) Elbow method and Gap Statistic are used together to determine the optimal number of clusters. (**C**) Changes in eGDR are classified into three classes. (**D**) Mean eGDR for the three classes in 2012 and 2015. Class 1 (Green) - Persistent High Group; Class 2 (Blue) - Rapidly Decreasing Group; Class 3 (Orange) - Persistent Low Group.

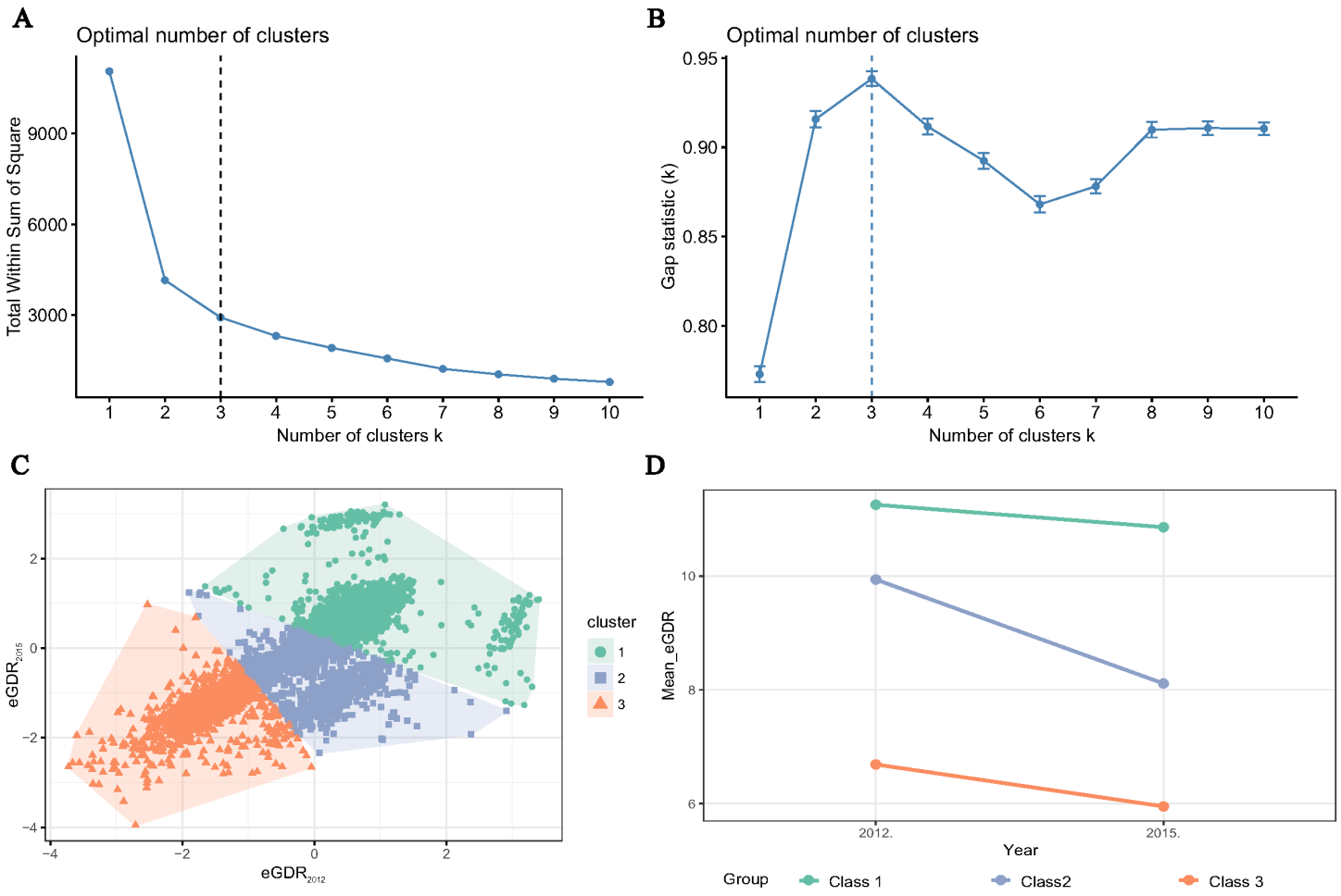
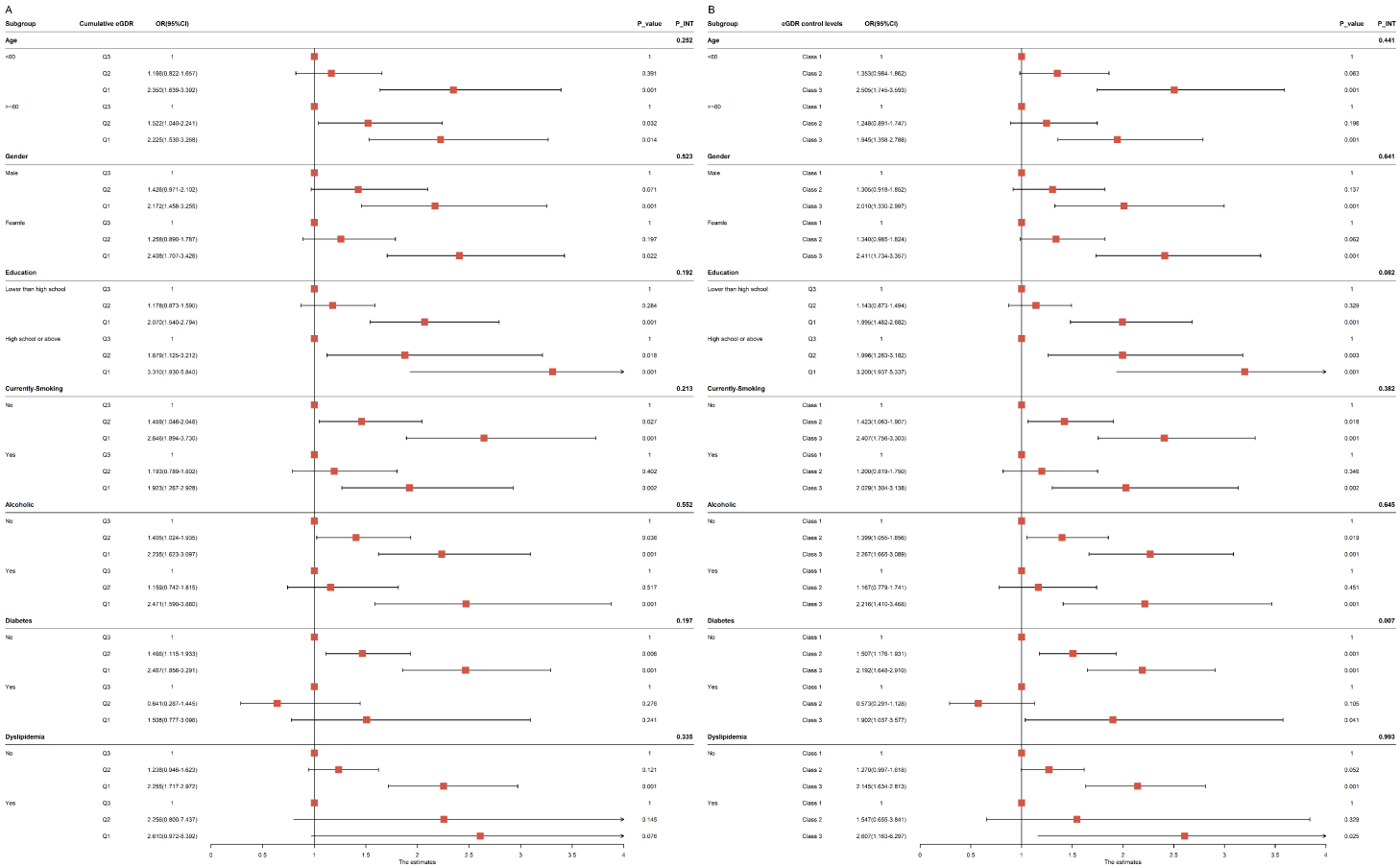


Figure 2

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Figure 3 | Forest plot of a subgroup analysis in Model 2. (**A**) Forest plot of subgroup analysis for Cumulative eGDR. (**B**) Forest plot of subgroup analysis for eGDR control levels.



Model2: Age+Gender+DM+Dyslipidemia+Currently smoking+Alcoholic+BMI+Education+ Household Register

Figure 3

See image above for figure legend

Figure4|Mediation analyses between the eGDR control levels and new-onset CVD in non-DM population. (A) Total cholesterol as a mediator between eGDR control levels and new-onset CVD. (B) Low density lipoprotein cholesterol as a mediator eGDR control levels and new-onset CVD.

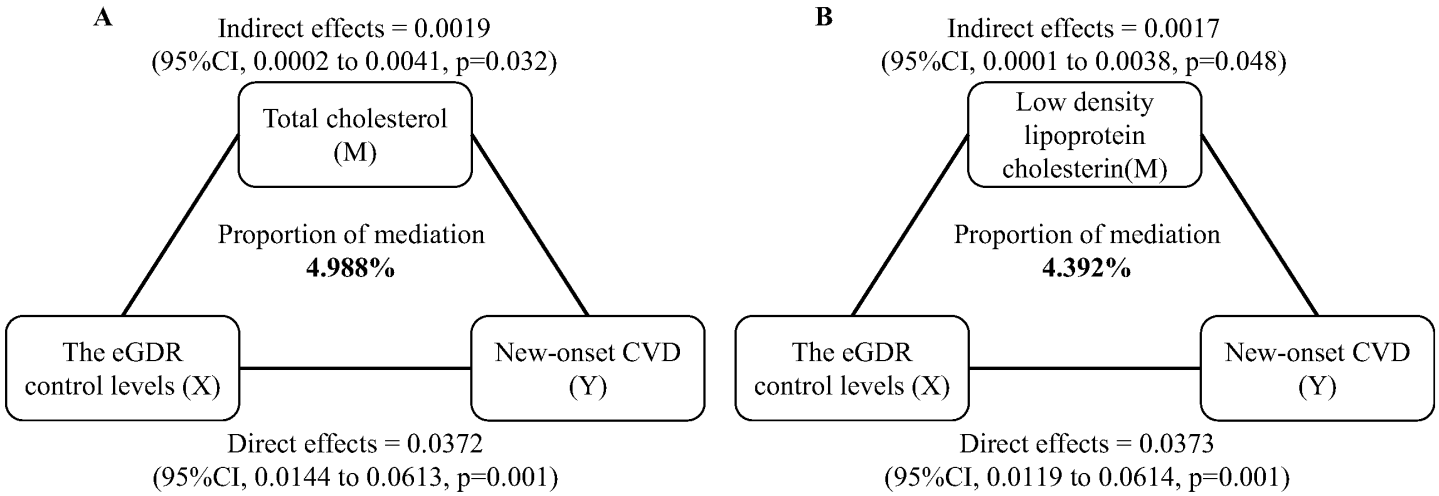


Figure 4

See image above for figure legend

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