Association of the Trajectories of Metabolic Component and Outcomes in Patients with Chronic Kidney Disease: The National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS) Study

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Abstract

Background: Chronic kidney disease (CKD) could cause and exacerbate metabolic disturbances, including hypertension and dyslipidemia. Conversely, metabolic disturbances affect renal outcome and mortality in CKD patients. However, studies on the relationship between the pattern of metabolic disturbance and prognosis in CKD during the observation period are lacking.

Methods: Through trajectory analysis, we found that subjects with CKD were divided into two groups in a pattern of metabolic disturbances over time. Subjects were divided into low (A) and high (B) groups using K-means clustering based blood pressure, total cholesterol (TC), triglyceride (TG), and low-density lipoprotein (LDL) cholesterol measurement at two time-points. The optimal number of clustering was selected using the Calinski-Harabasz index. The outcome of our study was a decline in renal function and mortality.

Results: This study is a large-scale retrospective study of 51,313 subjects with CKD from The National Health Insurance Service-National Health Screening Cohort. The mean age of the subjects was 65.7 ± 9.7 years, and 50.4% were male. During the study period, the mean systolic blood pressure (SBP) was 127.8 ± 15.8 mmHg and diastolic blood pressure (DBP) was maintained at 83.6 ± 8.4 mmHg. Mean serum LDL cholesterol and TG levels were 196.4 ± 40.9 and 147.1 ± 89.8 mg/dL, respectively. After clustering, the low group (A group) had the mean SBP of 118.9 ± 10.9 mmHg and a TG of 118.8 ± 46.1 mg/dl. However, in the high group (B group), it was found that the mean SBP was maintained at 138.9 ± 13.2 mmHg, and the TG was maintained at was 266.1 ± 116.7 mg/dL. In logistic regression analysis, the high group of SBP was associated with the decline of renal function and increased mortality (odds ratios [OR] 1.13 95% confidence intervals (CI) 1.066-1.212). and the high group of TG was independently associated with a decrease in renal function (OR 1.15, 95% CI 1.069-1.240).

Conclusion: The results of this study showed the association of the pattern of metabolic disturbances with the prognosis of CKD over time. Additionally, it could be useful to control intensively SBP for renal outcome and mortality in CKD, and management of high TG could be necessary to improve renal outcome.

Introduction

Chronic kidney disease (CKD) increases the risk of chronic metabolic illnesses, including hypertension (HTN), diabetes mellitus (DM), and hyperlipidemia [1, 2]. CKD also affects renal function deterioration reciprocally [3–5]. According to USRDS annual data report, HTN is the second most common cause of end-stage kidney disease in the US, followed by DM. Similar results of epidemiology has been reported in Korea. [6]. Prolonged high blood pressure causes a decrease in renal function [7]. Consequently, the deterioration in kidney function and renal fibrosis lead to increased blood pressure due to the accumulation of salt [8]. Although it is crucial to control blood pressure to reduce the mortality and incidence of cardiovascular disease in patients with HTN and CKD, the optimal blood pressure level is still

controversial [9]. Obesity is also associated with an increased risk of developing CKD [10, 11]. Obesity causes glomerular hyperfiltration [12], and unlike the general population, a reversal of the obesity-mortality association is observed in the CKD population [13]. CKD is associated with dyslipidemia from the early stages of microalbuminuria [14]. As proteinuria increases, total cholesterol (TC), very-low-density lipoprotein, low-density lipoprotein (LDL) cholesterol, and triglycerides (TG) also increase [15]. However, the ideal cholesterol values, including TG for CKD patients, have not been determined, and debates regarding optimal blood pressure and body mass index (BMI) has been continued.

One of the reasons why controversy persists is that the outcomes were inconsistent because of the reverse epidemiology in CKD patient. During the observation period, we tried to find whether these metabolic factors were individually trajected and to determine the effect of these trajectories on the outcome. To evaluate this, we used the National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS) performed over the last four years in South Korea.

Materials And Methods

The National Health insurance service and National Health screening in Korea

South Koreans are obliged to purchase health insurance. Thus, 97% of the population, excluding beneficiaries of the basic national livelihood and national meritorious persons, were covered for universal healthcare service. The National Health Insurance Database of Korea is a vast, informative resource that includes all Koreans who have health insurance. This database contains data on insured medical services, health screenings, and sociodemographic variables. In addition, information on hospital claims with the International Classification of Disease, 10th edition (ICD-10) coding and death was available. Through National Health Screening, Korean adults over the age of 40 were provided free general health screening once every 1-2 years [16, 17]. This study was approved by the Institutional Review Board of the Korea National Institute for Bioethics Policy (No. P01-201603-21-005), and written informed consent was waived, as this is a retrospective analysis of de-identified administrative data [16,17].

Study population

We screened adults aged 40 to 79 who underwent health screening from 2010 to 2013. A total of 866,310 screening examinations over four years were verified. Among 866,310 cases of screening, 51,313 patients with chronic kidney disease (CKD) who had undergone 2 and more screening were included final analysis from 2010 to 2013 (Total cases of screening test were 63,537 cases). The CKD is defined as a MDRD estimated GFR of less than 60 mL/min/1.73 m²

Definition of chronic diseases and study outcomes

The CKD was defined as a MDRD estimated GFR of less than 60 mL/min/1.73 m² body surface area. DM was defined as fasting plasma glucose levels $\geq$ 126 mg/dL at measurement or case with diagnostic code (the International Classification of Diseases, 10th Revision [ICD-10] codes E11–14) or prescription of antidiabetic medication. HTN was defined by blood pressure $\geq$ 140/90 mm Hg or case with diagnostic code (ICD-10 codes I10–I15) or prescription of antihypertensive medication. Dyslipidemia was defined by TC level $\geq$ 240 mg/dL or case with diagnostic code (ICD-10 code E78) or prescription of antihyperlipidemic medication. Cardiovascular disease was identified when the participant gave an affirmative answer to questionnaire. Cancer was defined by the presence of the specific diagnostic criteria for cancer and diagnosed and certified by a physician. The outcome of our study was all-cause mortality and a decrease in eGFR compared with the first screening between 2010 and 2013.

Statistical analysis

We divided and clustered participants into group-based trajectory modeling for comparing changeable aspect of metabolic component. For group comparisons, we used the t-test for continuous variables and the χ^2 test for proportions. Multivariate logistic regression analysis was applied for relative risk evaluation of all-cause mortality and renal outcomes. Cox regression analysis was used to calculate the hazard ratios (HRs) and 95% CIs for cluster variables. Principal component analysis of multivariate Gaussian distribution was used in exploratory data analysis. The dimension consists of the eigenvectors of the covariance matrix scaled by the square root of the eigenvalue. All variables trajectory modeling was as follows: To categorize the trend of SBP, DBP, TC, TG, LDL, BMI, serum creatinine over time, we applied group-based trajectory modeling using the kml package in R statistics. K-means is a hill-climbing algorithm belonging to the expectation-maximization class. First, each observation was assigned to one cluster. Then, the optimal clustering was completed by the alternation of two phases. (kml and kml3d: R Packages to Cluster Longitudinal Data. 2015, volume 65, issue 4. journal of statistical software) During the expectation phase, the centers between two different clusters were computed. And during the maximization phase, each observation was matched to the nearest cluster. For the initialization method, K-means used random partition. For complexity, K-means analysis used Euclidean distance to assign optimal distance. For the partitioning clustering plot, we used the factoextra package in R statistical software by using the Calinski-Harabasz index. In the resulting plot. All observations are represented by points using principal components.

Results

Baseline characteristics according to the year of screening from 2010 to 2013

The participants' average age was 65.7 ± 9.7 years, and 50.4% were male. The history of HTN, DM, and hyperlipidemia was 57.8%, 24.2%, and 9%, respectively. Further, among cardiovascular diseases, 4.1% reported cerebral infarction, and 10.9% had cardiac disease. The mean SBP of the participants were

127.8 ± 15.8 mmHg. Additionally, BMI and waist circumferences were 24.4 ± 3.0 kg/m² and 83.6 ± 8.4 cm, respectively. For kidney function, the serum creatinine was 2.4 ± 3.4 mg/dL, and Modification of Diet in Renal Disease (MDRD) eGFR was 46.0 ± 17.6 ml/min/1.73m². From 2010 to 2013, the examinee's age increased from 63.1±9.8 to 68.6±8.9 years, and the proportion of women gradually increased from 49.6% to 54.0%. The prevalence of HTN (from 51% to 30.9%), DM (from 82.7% to 65.7%), and hyperlipidemia (from 94.3% to 84.4%) showed a gradual decreasing pattern. As metabolic factors, the mean level of LDL and high-density lipoprotein (HDL) cholesterol decreased, and GFR increased. (Table 1).

Trajectory analysis of variables with a metabolic component within four years

In trajectory analysis, a mean maintenance level of SBP was 138.9±13.2 mmHg in cluster B and 118.9±10.9 mmHg in cluster A ($P<0.001$). DBP was maintained at a mean of 84±8.0 mmHg in cluster A, 71.3±7.3 mmHg in cluster B ($P<0.001$). In lipid profile, TC (167.5±26.6 mg/dL in cluster A, 223.4±33.0 mg/dL in cluster B, $P<0.001$), TG (118.8±46.1 mg/dL in cluster A, 266.1±116.7 mg/dL in cluster B, $P<0.001$), and LDL cholesterol (89.9±24.3 mg/dL in cluster A, 139.7±31.2 mg/dL in cluster B, $P<0.001$) were lower in cluster A than cluster B. BMI was clustered into five groups from A to E in the order of the number of distributions of the participants. Most participants maintained at 22 – 25.9 (BMI cluster A: 24.0±0.8 kg/m²; B: 25.9±0.9 kg/m²; C: 22.1±0.9 kg/m²; D: 28.2±1.1 kg/m²; E: 19.6±1.3 kg/m²; F: 31.9±2.2 kg/m², $P<0.001$, respectively) and it was 19.6±1.3 kg/m² at a value close to the criterion of underweight in BMI cluster E group. (Fig 1).

Difference comparison for cluster groups according to all-cause mortality

A total of 307 deaths occurred in clusters A and B from 2010 to 2013. Among the deceased, 233 cases (75.9%) were screened once during the study period. Ten cases (3.3%) had a screening interval of 1 year, 58 cases (18.9%) of 2 years, and six cases (2.0%) of 3 years. In survivors compared to the deceased, the proportion of participants who received screening only once during the study period was low and there were more cases where the screening interval was once a year. The difference in cluster group distribution between the deceased and survivor was compared; among the cluster variables, SBP, DBP, TC, and TG were not significantly different. Proportions of BMI cluster E was more in the deceased (event-free group: Cluster E 9.4%; event group cluster E 20.5%, respectively) (Table 2).

Difference comparison for cluster groups according to the decline of eGFR

There was no difference in the number of deaths in the GFR decrement group compared to the non-GFR decrement group. The interval between most participants' health screens was two years (59.2% in the non-GFR decrement group, 62.8% in the GFR decrement group). In the group with decreased renal function, eGFR change was 4.7 ± 6.9 ml/min/1.73m². Among the metabolic components, the proportions of SBP cluster B were 46.9% and 48.5%, respectively, which was higher in the GFR decrement group. The proportions of DBP cluster B were higher in the GFR decrement group (47.7% and 49.3%, respectively). In the GFR decrement group, TG cluster B were 20.9%, which was higher than the non-GFR decrement group. As for other factors, there was no significant difference between the two groups (Table 3).

Regression analysis for events using clustering variables

In logistic regression analysis, SBP cluster B and BMI cluster E were associated with all-cause mortality (SBP cluster B: OR 1.823, 95% CI 1.066-1.212, $P = 0.027$; BMI cluster E: OR 2.194, 95% CI 1.071-1.4.387, $P = 0.027$). Factors related to GFR decline included SBP cluster B (HR 1.130, 95% CI 1.066-1.212, $P < 0.001$), DBP cluster B (HR 1.105, 95% CI 1.036-1.178, $P = 0.002$), TG cluster A (OR 1.151, 95% CI 1.069-1.240, $P < 0.001$) showed a significant correlation (Table 4). In multivariable Cox regression analysis, it was not observed to increase in the hazard ratios in cluster B group according to the metabolic component except for BMI (Fig 2). However, we found a lower risk of mortality (HR 0.35, 95% CI 0.15-0.83) in the cluster D (BMI 28.2 ± 1.1 kg/m²) compared to the cluster A (24.0 ± 0.8 kg/m²) (Table 4).

Discussion

Our study is an observational study using data from the large-scale National Health Insurance Service-National Health Screening Cohort. This study showed the importance of controlling chronic diseases, including HTN and dyslipidemia, by performing trajectory cluster analysis on data obtained through continuous measurement of metabolic factors in the CKD patient group.

Blood pressure control in the CKD patient group is important for preventing CKD progression and mortality. However, controversy remains about the optimal blood pressure that can prevent renal function decline and improve mortality in CKD patients. Furthermore, most randomized controlled trials (RCTs) about blood pressure control have limitations that exclude or include only a small number of patients with CKD. In terms of mortality, results of the International Verapamil-Trandolapril Study suggest a possible J-curve relationship between blood pressure and mortality through previous observational studies [18]. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial in patients with Type 2 DM showed no improvement in all-cause mortality with the intensive control of SBP (< 120 mmHg) [19]. In a study including 77,765 CKD patients, the effect of intensive treatment compared to standard treatment (SBP < 120 vs $120-139$ mmHg) was not proven [20]. However, diabetic nephropathy patients with an SBP of 120 mmHg had the most protective cardiovascular event in the Irbesartan Diabetic Nephropathy Trial [21]. In terms of renal outcomes, studies on the effect of blood pressure control on renal function also show mixed results. Two representative studies for blood pressure control in CKD (the

MDRD study and African-American Study of Kidney Disease and Hypertension (AASK) study) did not demonstrate an improvement in CKD progression through intensive control [22, 23]. A meta-analysis and Renin-2 trial also reported that intensive control did not provide additional benefit for renal outcomes for CKD progression [24, 25]. However, the advantage of intensive treatment was highlighted through the SPRINT trial. [26]. The SPRINT Research Group reported that major cardiovascular events and all-cause death decreased in the intensive control group through subgroup analysis of 2,646 CKD patients [27]. In 2019, pooled analyses from 4 RCTs, including AASK, ACCORD, MDRD and the SPRINT, have been published demonstrating mortality benefits of SBP < 130 mmHg in CKD patients [28]. In the guideline for the management of blood pressure in CKD announced by KDIGO in 2021, it is suggested to control SBP < 120 mmHg if tolerable (2B) [29]. The mean SBP of the cohort participants included in our study was 127.8 ± 15.8 mmHg, which was well controlled compared to the standard concept. The cluster A group, controlled to mean 118.9 ± 10.9 mmHg, showed a lower risk of mortality and better renal outcome through trajectory analysis. This is consistent with the recently accepted trend in which the benefits of intensive control are highlighted.

Hyperlipidemia is a major risk factor for cardiovascular disease, and TG and HDL cholesterol are evaluated for metabolic syndrome. LDL cholesterol is the main therapeutic target for secondary prevention of atherosclerotic cardiovascular disease. CKD patients were classified as a high-risk group in the 2019 guideline of dyslipidemia in the European Society of Cardiology [30]. Dyslipidemia is associated with a decrease in renal function [31, 32]. In CKD patients, an increase in TG and LDL is commonly observed, and multiple lipid-lowering agents are often required [33]. Although it is emphasized to identify the lipid profile in CKD patients, the main therapeutic target is LDL cholesterol. In the SHARP trial, using a lipid-lowering agent could not reduce the risk of ESRD, nor did it reduce major atherosclerotic events in dialysis-dependent patients. [34]. In our study, the TG cluster A group (maintained the mean 118 ± 46.1 mg/dL) had a better renal outcome than the TG cluster B group with hypertriglyceridemia. This finding is consistent with the results of other cohort studies showing the need for control of hypertriglyceridemia in CKD patients [35]. Reverse epidemiology of the obesity paradox has been observed in chronic disease patients, including CKD patients [36, 37]. As observed in the general population, it is also known to increase the mortality rate of patients with low BMI. Low weight in CKD patients, including those dependent on dialysis, is closely related to protein-energy wasting syndrome [38, 39], a major cause of increased mortality [40]. Although most of the participants in our study maintained a BMI of 22-24 kg/m², the risk of death in the cluster E group increased. This result suggests that it is important to improve the nutritional status of patients with low body weight. In cox regression analysis, our results showed that the mortality risk of cluster D was lower than those of cluster A. These findings are thought to reflect reverse epidemiology of the obesity paradox.

Korean citizens are registered for mandatory health insurance and could have health screen every 1-2 years. Through database containing many subjects, many studies have been conducted. Among the representative studies on metabolic syndrome, there is a study that showed the relationship between changes in metabolic syndrome status and prognosis [41]. However, the effect of changes in individual

factors of metabolic syndrome was not confirmed. We used Korean large-scale cohort database. Trajectory analysis was performed for each item of metabolic syndrome, and the effect of trajectory factors on the outcome of CKD was confirmed. Our study has some limitations. As a retrospective observational study, there is a possibility that the selection and lead-time bias of participants in the cohort may be involved. Additional confounding factors, such as differences in drugs taken by participants and the causative disease of CKD, may remain in relation to the mortality and renal outcome.

Conclusion

In conclusion, prolonged hypertension, glucose, hyperlipidemia have negative impacts on GFR confirmed by trajectory analysis. Cluster B has lower GFR than cluster A; this is caused by patients with chronic diseases in cluster B having not been controlled over four years as values of BMI, SBP and DBP. To not affect the function of the kidney, chronic diseases including HTN, DM, and hyperlipidemia need to be effectively controlled.

Abbreviations

ACCORD Action to Control Cardiovascular Risk in Diabetes

CI Confidence intervals

CKD Chronic kidney disease

DM Diabetes mellitus

DBP Diastolic Blood Pressure

ESKD End-stage kidney disease

GFR Glomerular filtration rate

HR Hazard ratios

HTN Hypertension

INVEST International Verapamil-Trandolapril Study

KORDS Korean Renal Data System

LDL Low-density lipoprotein

MDRD Modification of Diet in Renal Disease

NHIS National Health Screening

PCA Partitioning component of analysis

RCT Randomized controlled trials

SBP Systolic and diastolic blood pressure

TC Total cholesterol

VLDL Very-low-density lipoprotein

AASK African-American Study of Kidney Disease and Hypertension study

BMI Body mass index

ESKD End stage kidney disease

HDL High density lipoprotein

KDIGO The Kidney Disease: Improving Global Outcomes

SHARP Study of Heart and Renal Protection

SPRINT Systolic Blood Pressure Intervention Trial

USRDS United States Renal Data System

Declarations

Ethics approval and consent to participate

This study complied with the Declaration of Helsinki and was approved by the Institutional Review Board of the Korea National Institute for Bioethics Policy (No. P01–201603–21-005), and written informed consent was waived, as this is a retrospective analysis of de-identified administrative data.

Consent for publication

N/A

Availability of data and materials

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

Competing interests

None

Funding

None

Authors' contributions

Research idea and study design: KDY, HK; data acquisition: HH, JHS, GSK, KDY, YK; data analysis/interpretation: HH, JHS, HK, KDY, Each author contributed important intellectual content during manuscript drafting. All authors read and approved the final manuscript.

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Tables

Table 1

Baseline characteristics according to the year of screening from 2010 to 2013

	Total	2010	2011	2012	2013	<i>P</i>
	(N=63537)	(N=18772)	(N=17282)	(N=13283)	(N=14200)	
AGE (years)	65.7 ± 9.7	63.1 ± 9.8	65.4 ± 9.6	66.6 ± 9.3	68.6 ± 8.9	<0.001
Sex (%)						<0.001
Male	32030 (50.4%)	10136 (54.0%)	8758 (50.7%)	6598 (49.7%)	6538 (46.0%)	
Female	31507 (49.6%)	8636 (46.0%)	8524 (49.3%)	6685 (50.3%)	7662 (54.0%)	
Smoking history						<0.001
Non-smoker	42812 (67.9%)	12069 (65.3%)	11584 (67.4%)	9050 (68.3%)	10109 (71.3%)	
Ex-smoker	12800 (20.3%)	3847 (20.8%)	3577 (20.8%)	2700 (20.4%)	2676 (18.9%)	
Current smoker	7470 (11.8%)	2554 (13.8%)	2027 (11.8%)	1494 (11.3%)	1395 (9.8%)	
Alcohol history	1.7 ± 1.4	1.8 ± 1.5	1.7 ± 1.4	1.6 ± 1.4	1.6 ± 1.3	<0.001
Hypertension History						<0.001
No	22184 (42.2%)	8209 (51.9%)	6640 (45.2%)	3792 (35.6%)	3543 (30.9%)	
Yes	30416 (57.8%)	7593 (48.1%)	8039 (54.8%)	6848 (64.4%)	7936 (69.1%)	
Diabetes mellitus History						<0.001
No	36666 (75.8%)	13012 (82.7%)	11396 (78.8%)	6097 (69.1%)	6161 (65.7%)	
Yes	11735 (24.2%)	2724 (17.3%)	3067 (21.2%)	2726 (30.9%)	3218 (34.3%)	
Hyperlipidemia History						<0.001
No	42425 (91.0%)	14835 (94.3%)	13385 (93.1%)	7038 (87.7%)	7167 (84.4%)	
Yes	4190 (9.0%)	891 (5.7%)	990 (6.9%)	986 (12.3%)	1323 (15.6%)	
Total cholesterol (mg/dL)	196.4 ± 40.9	199.8 ± 40.2	196.6 ± 40.3	194.7 ± 41.1	193.5 ± 42.1	<0.001
Triglycerides	147.1 ±	150.3 ±	145.2 ±	146.2 ±	145.9 ±	<0.001

(mg/dL)	89.8	97.1	86.6	88.2	85.0	
HDL cholesterol (mg/dL)	53.9 ± 36.3	59.1 ± 61.0	51.9 ± 14.7	52.2 ± 20.1	51.0 ± 16.6	<0.001
LDL cholesterol (mg/dL)	115.5 ± 37.2	118.3 ± 37.6	115.5 ± 36.3	113.9 ± 37.1	113.5 ± 37.5	<0.001
Cerebral infarction History						<0.001
	44054 (95.9%)	15264 (97.2%)	13839 (96.4%)	7356 (94.7%)	7595 (93.7%)	
	1876 (4.1%)	445 (2.8%)	510 (3.6%)	410 (5.3%)	511 (6.3%)	
Heart disease History						<0.001
	41557 (89.1%)	14497 (92.2%)	12994 (90.3%)	6954 (85.9%)	7112 (84.0%)	
	5103 (10.9%)	1220 (7.8%)	1395 (9.7%)	1137 (14.1%)	1351 (16.0%)	
BMI (kg/m ²)	24.4 ± 3.0	24.3 ± 3.0	24.4 ± 3.0	24.4 ± 3.1	24.4 ± 3.1	<0.001
Waist (cm)	83.6 ± 8.4	83.4 ± 8.2	83.6 ± 8.3	83.6 ± 8.7	83.8 ± 8.6	<0.001
SBP (mmHg)	127.8 ± 15.8	127.3 ± 15.4	128.2 ± 16.0	128.1 ± 16.0	127.8 ± 15.6	0.003
DBP (mmHg)	77.6 ± 10.0	78.0 ± 9.9	77.8 ± 10.0	77.6 ± 10.2	77.0 ± 10.0	<0.001
FBS (mg/dL)	106.1 ± 31.0	104.6 ± 29.4	105.6 ± 29.9	106.8 ± 31.4	108.1 ± 33.9	<0.001
Hemoglobin (g/dL)	13.4 ± 1.7	13.6 ± 1.7	13.4 ± 1.7	13.3 ± 1.7	13.2 ± 1.7	<0.001
Creatinine (mg/dL)	2.4 ± 3.4	3.3 ± 4.0	2.7 ± 3.7	1.8 ± 2.7	1.6 ± 2.2	<0.001
MDRD eGFR	46.0 ± 17.6	41.4 ± 21.1	44.2 ± 19.1	49.9 ± 13.0	50.5 ± 11.6	<0.001

HDL, high density lipoprotein; LDL, low density lipoprotein; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; eGFR. estimated glomerular filtration rate

Table 2

Difference comparison for cluster groups according to all-cause mortality

	Survivor	Deceased	<i>P</i>
	(N=63230)	(N=307)	
Interval of screening			0.000
Once screened	39210 (62.0%)	233 (75.9%)	
1 year	6056 (9.6%)	10 (3.3%)	
2 years	14789 (23.4%)	58 (18.9%)	
3 years	3175 (5.0%)	6 (2.0%)	
SBP clusters			0.161
A	12503 (52.1%)	32 (43.2%)	
B	11509 (47.9%)	42 (56.8%)	
DBP clusters			0.744
A	12300 (51.2%)	36 (48.6%)	
B	11712 (48.8%)	38 (51.4%)	
TC clusters			0.918
A	12963 (54.0%)	39 (52.7%)	
B	11053 (46.0%)	35 (47.3%)	
TG clusters			0.471
A	19111 (79.7%)	62 (83.8%)	
B	4858 (20.3%)	12 (16.2%)	
LDL clusters			0.954
A	12305 (53.8%)	40 (54.8%)	
B	10580 (46.2%)	33 (45.2%)	
BMI clusters			0.007
A	6750 (28.1%)	19 (26.0%)	
B	5725 (23.8%)	14 (19.2%)	
C	5378 (22.4%)	20 (27.4%)	
D	3161 (13.2%)	3 (4.1%)	
E	2247 (9.4%)	15 (20.5%)	
F	754 (3.1%)	2 (2.7%)	

Table 3

Difference comparison for cluster groups according to the decline of eGFR

	No decrement (N=7803)	Decrement (N=16291)	<i>P</i>
Death			0.540
Survivor	7782 (99.7%)	16238 (99.7%)	
Deceased	21 (0.3%)	53 (0.3%)	
Change of eGFR (ml/min/1.73m ²)	-8.5 ± 11.8	4.7 ± 6.9	0.000
Interval of screening			0.000
1 year	2134 (27.3%)	3932 (24.1%)	
2 years	4621 (59.2%)	10226 (62.8%)	
3 years	1048 (13.4%)	2133 (13.1%)	
SBP clusters			0.023
A	4143 (53.1%)	8392 (51.5%)	
B	3658 (46.9%)	7893 (48.5%)	
DBP clusters			0.025
A	4077 (52.3%)	8259 (50.7%)	
B	3724 (47.7%)	8026 (49.3%)	
TC clusters			0.392
A	4180 (53.6%)	8822 (54.2%)	
B	3623 (46.4%)	7465 (45.8%)	
TG clusters			0.001
A	6300 (81.0%)	12873 (79.1%)	
B	1474 (19.0%)	3396 (20.9%)	
LDL clusters			0.650
A	3881 (54.0%)	8464 (53.7%)	
B	3306 (46.0%)	7307 (46.3%)	
BMI_clusters			0.901
A	2223 (28.5%)	4546 (27.9%)	
B	1866 (23.9%)	3873 (23.8%)	

C	1727 (22.1%)	3671 (22.5%)
D	1028 (13.2%)	2136 (13.1%)
E	720 (9.2%)	1542 (9.5%)
F	239 (3.1%)	517 (3.2%)

SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; LDL, low density lipoprotein; BMI, body mass index; eGFR, estimated glomerular filtration rate

Table 4

Logistic regression analysis for events using clustering variables

Death	beta	OR	<i>p</i> -value	95%CI
SBP clusters B (Ref. cluster A)	0.601	1.823	0.027	1.066~1.212
DBP clusters B (Ref. cluster A)	0.283	1.327	0.294	0.780~2.253
TC clusters B (Ref. cluster A)	0.272	1.312	0.442	0.893~1.055
TG clusters A (Ref. cluster B)	0.202	1.223	0.553	0.652~2.511
LDL clusters A (Ref. cluster B)	0.194	1.214	0.581	0.611~2.417
BMI Ref. cluster A				
BMI clusters B	-0.153	0.858	0.664	0.909~1.063
BMI clusters C	0.270	1.310	0.401	0.694~2.479
BMI clusters D	-1.117	0.327	0.072	0.889~1.072
BMI clusters E	0.785	2.194	0.027	1.071~4.387
BMI clusters F	-0.132	0.876	0.859	0.851~1.191
GFR decline	beta	OR	<i>p</i> -value	95%CI
SBP clusters B (Ref. cluster A)	0.128	1.130	<0.001	1.066~1.212
DBP clusters B (Ref. cluster A)	0.100	1.105	0.002	1.036~1.178
TC clusters B (Ref. cluster A)	0.029	1.029	0.492	0.947~1.119
TG clusters A (Ref. cluster B)	0.141	1.151	<0.001	1.069~1.240
LDL clusters A (Ref. cluster B)	0.045	1.046	0.279	0.963~1.136
BMI Ref. cluster A				
BMI clusters B	-0.016	0.983	0.680	0.909~1.063
BMI clusters C	0.027	1.027	0.680	0.949~1.112
BMI clusters D	-0.023	0.976	0.618	0.889~1.072
BMI clusters E	0.038	1.039	0.474	0.935~1.155
BMI clusters F	0.005	1.005	0.945	0.851~1.191
SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; LDL, low density lipoprotein; BMI, body mass index; eGFR. estimated glomerular filtration rate				

Figures

Figure 1

Trajectory analysis for the component of metabolic syndrome using NHIS-HEALS data In trajectory modeling, we divided subjects into two clusters according to variables of their metabolic components during study period. Cluster A is shown in red and cluster B is shown in light blue. (A) Systolic blood pressure (mean 118.9 ± 10.9 mmHg in cluster A, 138.9 ± 13.2 mmHg in cluster B, $P < 0.001$); (B) Diastolic blood pressure (84 ± 8.0 mmHg in cluster A, 71.3 ± 7.3 mmHg in cluster B, $P < 0.001$); (C) Total cholesterol (167.5 ± 26.6 mg/dL in cluster A, 223.4 ± 33.0 mg/dL in cluster B, $P < 0.001$); (D) Triglyceride (18.8 ± 46.1 mg/dL in cluster A, 266.1 ± 116.7 mg/dL in cluster B, $P < 0.001$); (E) Low density lipoprotein (89.9 ± 24.3 mg/dL in cluster A, 139.7 ± 31.2 mg/dL in cluster B, $P < 0.001$); (F) Body mass index (cluster A: 24.0 ± 0.8 kg/m²; B: 25.9 ± 0.9 kg/m²; C: 22.1 ± 0.9 kg/m²; D: 28.2 ± 1.1 kg/m²; E: 19.6 ± 1.3 kg/m²; F: 31.9 ± 2.2 kg/m², $P < 0.001$)

Hazard ratios of all variables

Figure 2

Forest plot for Cox regression analysis according to the trajectory group Hazard ratios of all variables for all-cause mortality