# Effect of the duration of ideal cardiovascular health metrics on the risk of chronic kidney disease and cardiovascular disease

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So Mi Cho

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This certifies that the dissertation of ***So Mi Cho*** is approved.

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The Graduate School
Yonsei University
December 2020

*Two roads diverged in a wood, and I—*

*I took the one less traveled by,*

*And that has made all the difference.*

—From “The Road Not Taken” by Robert Frost

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And to those whose names I hold dearly in my heart,
you are the best in me.

**December, 2020**

**So Mi Jemma Cho**

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## ABSTRACT

# Effect of the duration of ideal cardiovascular health metrics on the risk of chronic kidney disease and cardiovascular disease

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**(Directed by Professor Hyeon Chang Kim, MD, PhD)**

**Introduction:**

Increasing number of clinical guidelines are adopting comprehensive cardiovascular risk assessment tools for treatment decision and disease management in the context of primary and secondary prevention. Yet, little is

known regarding the exact cardiovascular risks associated with the length of favorable cardiometabolic health sustenance in midlife.

**Methods:**

From the Korean Genome and Epidemiology Study Ansung-Ansan cohort, we included 7,854 middle-aged adults without chronic kidney disease and 7,796 without cardiovascular disease at baseline. Duration of ideal cardiovascular health was the sum of time spent with ideal body mass index, blood pressure, fasting glucose, total cholesterol, cigarette smoking, alcohol drinking, and physical activity levels. We employed Cox proportional hazards model to assess chronic kidney disease and cardiovascular events risks.

**Results**:

The median age of the participants was 50.0 years and 47.9% were male. Over a median follow-up of 15.0 years, 1,401 new chronic kidney disease and 493 new cardiovascular disease occurred. With <5 years group as the reference, multivariable-adjusted hazard ratios [95% confidence intervals] for chronic kidney disease were 0.63 [0.39-0.93] with 5 to 10 years and 0.33 [0.15-0.74] with ≥10 years of ideal cardiovascular health (*P* trend, 0.0057). Similarly, participants lived with longer ideal cardiovascular health had significantly lower cardiovascular disease (5 to 10 years, 0.83 [0.54-1.27]; ≥10 years, 0.22 [0.08-0.60]). Subtype-specific analyses indicated negatively graded risks for coronary artery disease (*P* trend, 0.0239) and cerebrovascular disease (*P* trend, 0.0514).

**Conclusion:**

Our findings confer that maintaining favorable health behaviors and clinical cardiometabolic profile in midlife will improve later-life cardiovascular outcomes.

**Keyword:**

cardiovascular disease; chronic kidney disease; risk factor; cumulative risk; trajectory

# I. Introduction

In 2010, the American Heart Association has released cardiovascular health (CVH) metrics called the "Life's Simple 7"[1] based on established, modifiable, clinical and lifestyle risk factors. In align, various international clinical guidelines[2-4] have adopted and actively utilized comprehensive atherosclerotic cardiovascular disease risk assessment algorithms that account for total burden of risk rather than weighing on a specific risk factor. Such holistic tools are intended to aid long-term monitoring and managing of cardiovascular disease (CVD), the leading cause of mortality worldwide.[5] Beyond, timely and sustained management is expected to curtail life-years lost, improve quality of life, and conserve direct and indirect healthcare costs.[6]

Previous clinical trials and epidemiological studies have demonstrated the individual benefits of curbing obesity pandemic,[7] blood pressure,[8] cholesterol,[9] and blood sugar[10]-lowering, smoking cessation,[11] moderate alcohol consumption,[12] and regular physical activity[13] in the context of both primary and secondary prevention of CVD. Recent observational studies have illustrated the association between a single-occasion, composite CVH measure and subclinical atherosclerosis based on coronary artery calcium progression[14] and cardiac troponin T reduction.[15] However, growing literature[16,17] underscores the novelty of repeated measures over long time, as they can reflect lifetime burden.

Little is known on the risk magnitude associated with duration spent with optimal cardiometabolic profile in middle-age, Korean population. Considering the stabilized heart diseases mortality rate in recent Korean population,[18] evaluating whether longer time spent in ideal CVH is associated with risk of target organ damage and hard cardiovascular events may help to resolve its stagnancy. Specifically, it may incentivize clinicians and patients to adopt favorable lifestyle and to adhere to pharmacological treatment.

In this context, we examined whether the duration of ideal CVH, based on including body mass index, blood pressure, blood glucose, total cholesterol, cigarette smoking, alcohol drinking, and physical activity, in middle-age is associated with risk of developing chronic kidney disease (CKD) and CVD in mid-to-late-life. To address this aim, we analyzed data from the Korean Genome and Epidemiology Study (KoGES) Ansung-Ansan, an ongoing, community-based, prospective cohort in Republic of Korea.

# II. Methods

## 1. Study population

The KoGES consortium is a platform designated to investigate the genetic, social, and environmental etiology of common chronic diseases (i.e., hypertension, obesity, cancer) and mortality in Republic of Korea.[19] Ultimately, it intends to illustrate distributions of risk factors and, thereby, to develop all-inclusive and feasible clinical guidelines.[19] To do so, it collected detailed information on demographics, morbidity, lifestyle, diet, and healthcare utilization and provided comprehensive anthropometric, blood, and urinal profiles from on-site health examination. The details of the KoGES is published elsewhere.[19] The characteristics of the KoGES participants are comparable to that of the nationwide sample from the Korea National Health and Nutrition Examination Survey and the national cancer statistics.[20]

For this study, we selected the KoGES Ansung-Ansan, an ongoing community-based, prospective cohort in the two suburban cities. Based on a two-stage cluster sampling recruitment method, 10,030 participants, aged 40-69 years, underwent baseline examination between 2001 and 2002. The KoGES Ansung-Ansan study was administered, reviewed, and approved by the Korea Center for Disease Control and Prevention. All participants had voluntarily participated and provided written informed consent. The present study was approved by the

Institutional Review Board of Yonsei University Health System (Y-2020-0007) and was conducted in accordance with the Declaration of Helsinki.

Among 10,030 participants, 912 participants who had not attended any of the seven follow-up examinations were excluded. Then, 1,098 participants with missing information on CVH metrics, including body mass index, blood pressure, fasting glucose, total cholesterol, cigarette smoking, alcohol drinking, or physical activity, were further excluded. Of the remaining 8,020 participants, 166 participants with CKD at the baseline were excluded in the final analyses with CKD as the outcome; analogously, 224 participants with CVD at the baseline were excluded when the outcome of interest was CVD (Figures 1&2).

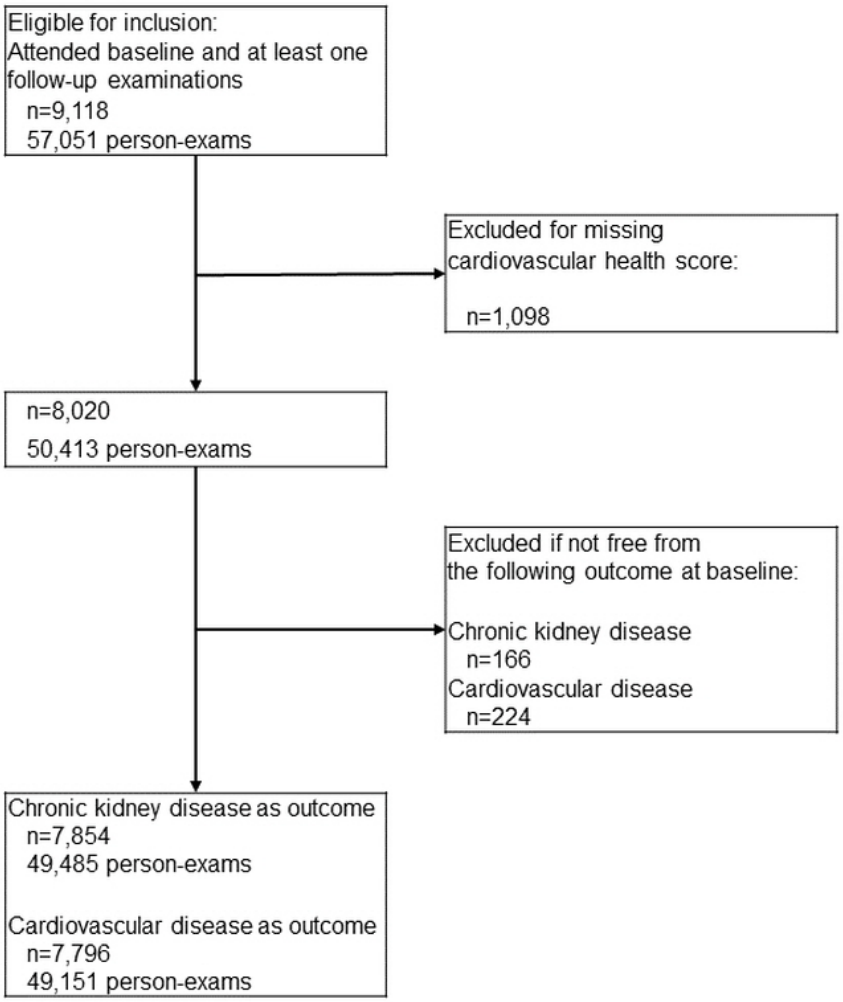


**Figure 1. Derivation of study population**

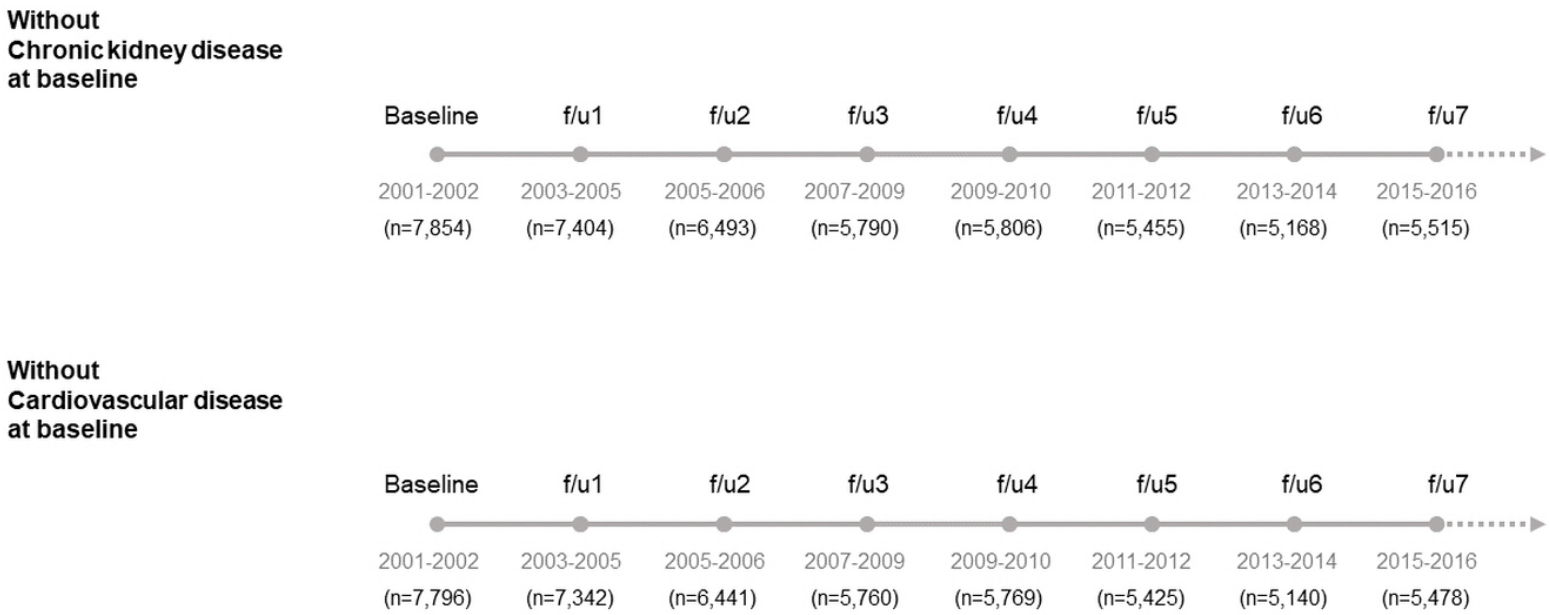


**Figure 2. Attendance at baseline and follow-up examinations**

## 2. Measurements

### A. CVH metrics

Quality of the survey and health examination was controlled by trained personnel using calibrated equipment and strictly adhering to standardized protocols and manufacturers' recommendations.

Body mass index was assessed via multifrequency bioelectrical impedance analysis while wearing light clothing without shoes (InBody 3.0, Biospace, Seoul, Korea). Based on the Asia-Pacific classification from the World Health Organization guideline,[21] we categorized the participants into normal (<23 kg/m$^2$), overweight (23-25 kg/m$^2$), or obese (≥25 kg/m$^2$). Blood pressure was measured on two consecutive occasions at 1-minute intervals using a standard mercury sphygmomanometer. In a standardized environment, participants had seated rest for five minutes and had refrained from smoking or food consumption prior to the measurement. To minimize variability and misclassification due to white coat hypertension, the averaged value was adopted for the data analysis. The participants were classified into having (1) untreated systolic blood pressure/diastolic blood pressure <120/80 mmHg, (2) untreated systolic blood pressure 120-130 mmHg and diastolic blood pressure <90 mmHg or treated to the ideal blood pressure, or (3) systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. Eight-hour fasting glucose and total cholesterol concentrations were enzymatically assessed via Hitachi Automatic Analyzer 747

(Hitachi Ltd., Tokyo, Japan). The participants were classified into having untreated serum total cholesterol >200 mg/dL, untreated 200-240 mg/dL or treated to ideal, or ≥240 mg/dL. Likewise, the participants were scored based on fasting glucose levels of <100 mg/dL (untreated), 100-126 mg/dL (untreated) or treated to ideal, or ≥126 mg/dL.

Based on a structured questionnaire, trained researchers conducted face-to-face interview on previous physician diagnosis and current pharmacological treatment of hypertension, diabetes mellitus, dyslipidemia, CKD, CVD, and more. Education level was categorized into completion of elementary school or below, middle school, high school, or completion of higher education. Regarding lifestyle, the participants were asked to report their current cigarette smoking status, which was classified as never, former, or current. Here, former smoker included those who had ceased smoking for 12 consecutive months or longer. Next, the participants reported current drinking status; if currently drinking, they were asked to report the average number of each type of alcoholic beverage consumed per week. We classified the participants based on the quantify of consumption: 0, 1-2 drink(s) per week, or 3+ drinks per week. Regarding physical activity, the participants were asked to report average number of days and duration of moderate-to-vigorous intensity, leisure-time physical activities performed per week. Examples of moderate-to-vigorous physical activity include fast-pace jogging, swimming, and tennis, which are rigorous enough to secrete sweat. Based on the guideline[22] recommendation, participants were categorized into sedentary (0 min/week of moderate or vigorous physical activity), insufficiently active (0 to

149 min/week of moderate physical activity or 0 to 74 minutes/week of vigorous physical activity), or active (150+ min/week of moderate physical activity or 75+ min/week of vigorous physical activity).

Altogether, the aforementioned clinical and lifestyle CVH metrics were summed to yield a composite CVH score for each examination. For each metric, 0 (poor), 1 (intermediate), or 2 (ideal) point(s) were assigned (Table 1). Based on the sum of seven metrics, scores of 0 to 7, 8 to 11, or 12 to 14 points were regarded as having poor, intermediate, or ideal CVH, respectively.

**Table 1. Definition and scoring of each cardiovascular health metrics**

| Metrics | Poor (0 point) | Intermediate (1 point) | Ideal (2 points) |
|---|---|---|---|
| Cigarette smoking | Current smoker | Former smoker | Never smoker |
| Alcohol drinking | ≥3 drinks/week | 1-2 drink(s)/week | Non-drinker |
| Physical activity | 0 minutes | More than 0 minutes<br>but less than the recommendations | 75+ min of vigorous activity or<br>150+ min of moderate-vigorous activity |
| Body mass index | ≥25 kg/$m^2$ | 23-25 kg/$m^2$ | <23 kg/$m^2$ |
| Blood pressure | SBP ≥140 mm Hg or DBP ≥90 mm Hg | SBP 120-139 mm Hg,<br>DBP <90 mm Hg,<br>or treated to ideal | <120/80 mm Hg (untreated) |
| Fasting plasma glucose | ≥126 mg/dL | 100-126 mg/dL or treated to ideal | <100 mg/dL (untreated) |
| Total cholesterol | ≥240 mg/dL | 200-240 mg/dL or treated to ideal | <200 mg/dL (untreated) |

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure

**B. Ideal CVH duration**

The number of years lived in ideal CVH category was calculated as the sum of duration with ideal CVH score between each examination. If a participant had not attended a particular follow-up examination, we calculated the duration based on the most recently attended examination prior to that absent one by linearly regressing the score—referred as the *regressed model* (Figures 3A&B). For example, if a person B scored 14 (ideal) at the 2$^{nd}$ follow-up, did not attend the 3$^{rd}$ follow-up, and scored 11 (intermediate) at the 4$^{th}$ follow-up (60 months from the 2$^{nd}$ follow-up), he/she would hypothetically maintain ideal CVH for 40 months since the 2$^{nd}$ follow-up, which thereafter, the score would deteriorate below the ideal threshold.

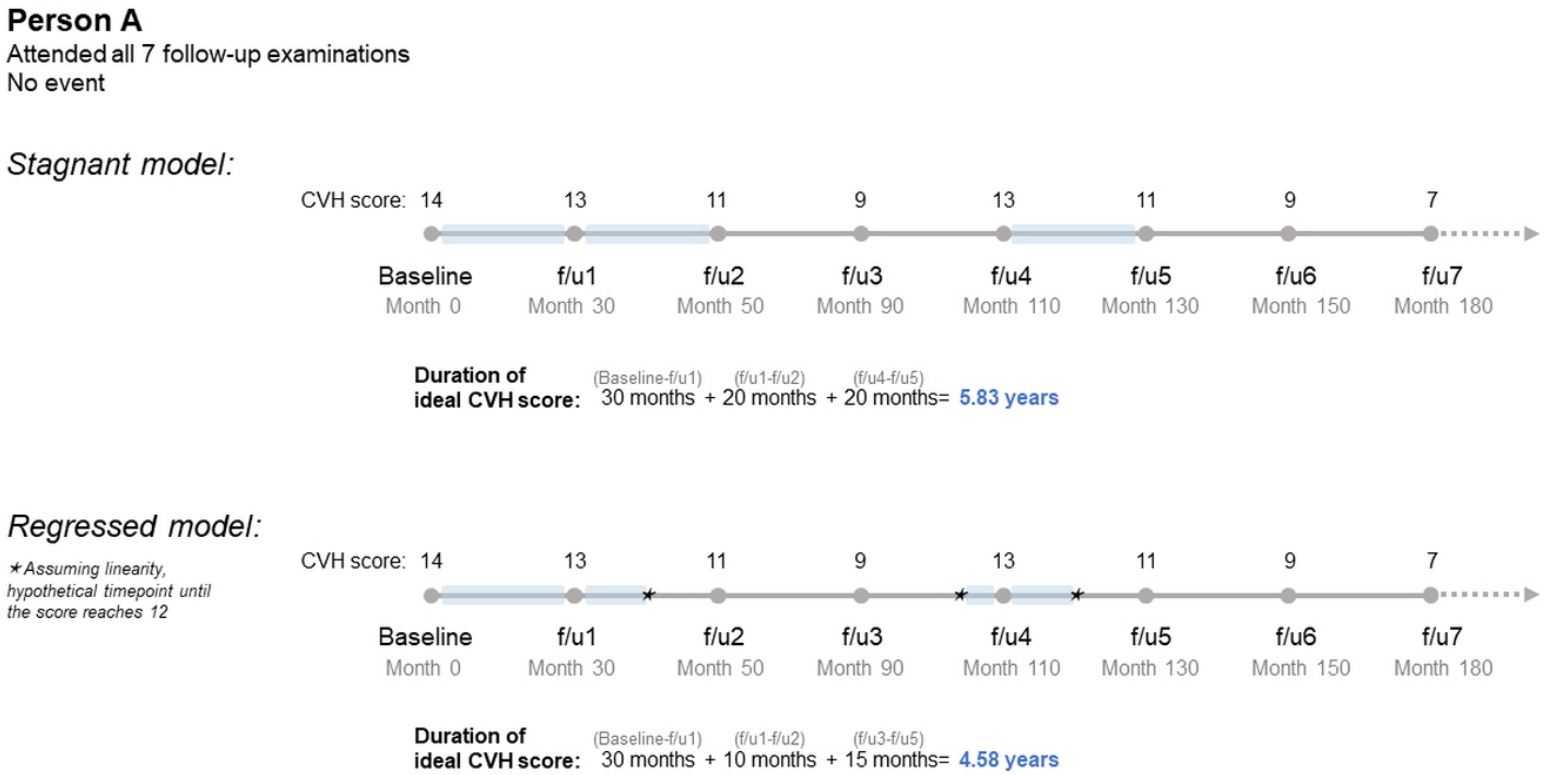


**Figure 3A. Example of ideal cardiovascular health (CVH) duration calculation in a participant who has attended all follow-up examinations**

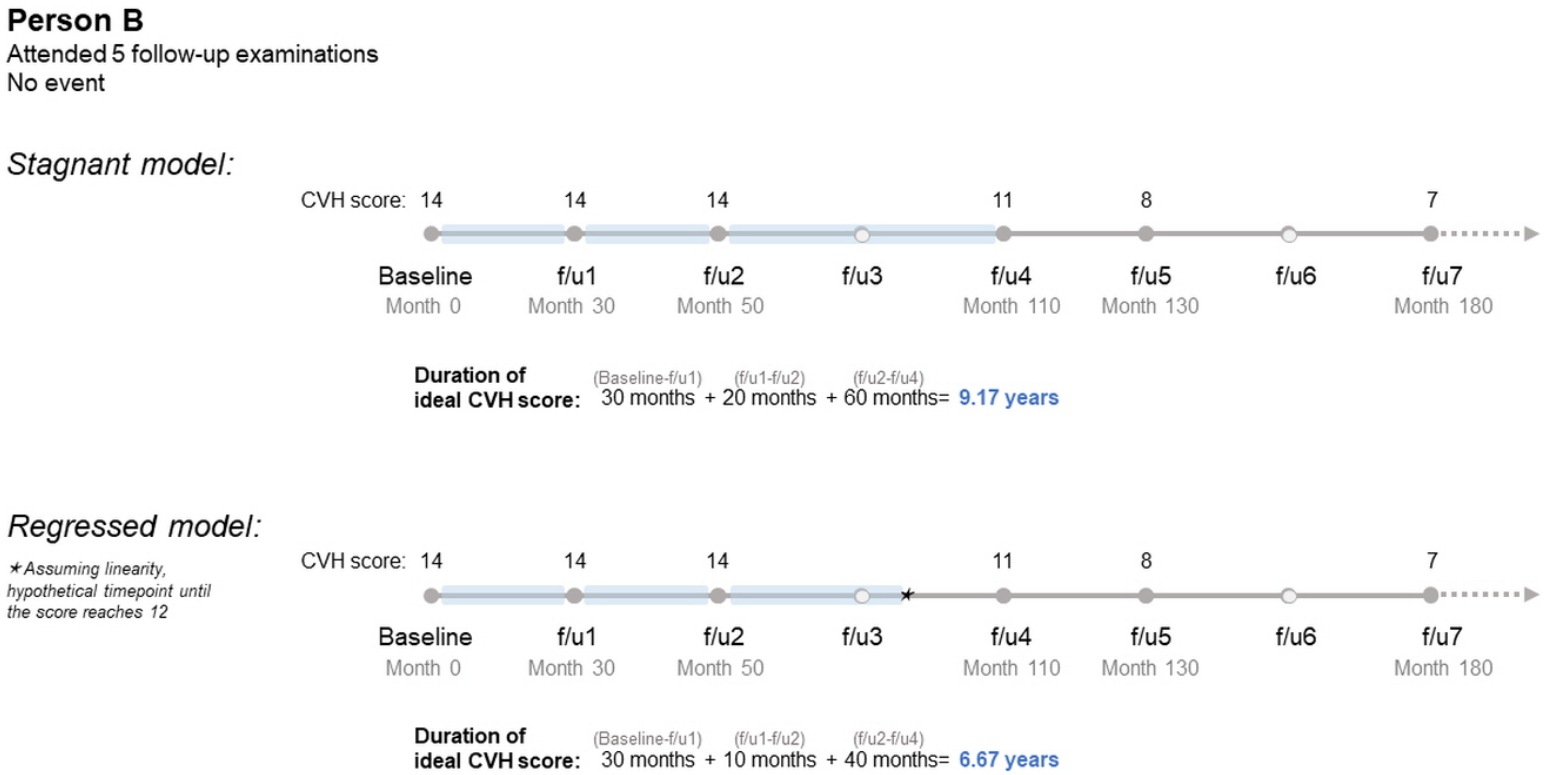


**Figure 3B. Example of ideal cardiovascular health (CVH) duration calculation in a participant who has attended only 5 follow-up examinations**

**C. Outcomes**

For each examination, the participants underwent chemistry test after overnight fasting for a minimum of 8 hours. Urine albumin level was obtained from a 10 ml midstream spot urine sample and was analyzed using URISCAN Pro II (YD Diagnostics, Seoul, Korea). Serum creatinine level was measured with an isotope-dilution mass spectrometry traceable method based on rate-blanked compensated Jaffe kinetic assay[23] using ADVIA 1650 (Siemens, Tarrytown, NY, USA). Estimated glomerular filtration rate (eGFR) was calculated from the serum creatinine level based on the Chronic Kidney Disease-Epidemiology Collaboration equation;[24] CKD was defined as having an eGFR <60 ml/min/1.73m$^2$ or self-reported physician diagnosis or treatment.[25] Urine albumin-to-creatinine ratio (UACR) was defined as a ratio of the urine albumin (mg/dL) to creatinine (g/dL) concentrations.

CVD was defined based on a self-reported physician diagnosis for coronary artery disease, cerebrovascular disease, or heart failure. If a participant had >1 different type of event, the first event of each type was counted as an outcome. For example, if a participant had coronary artery disease and then had a heart failure a year later, both coronary artery disease and heart failure were counted as separate outcomes in the end point, subtype-specific analyses.

### 3. Statistical analyses

General characteristics of the study participants were reported as frequency and percentage or mean and standard deviation. We compared the differences in demographics and physiological characteristics across participants with ≥10 years, 5 to 10 years, or less than 5 years of ideal CVH score. Next, we delineated the distribution of ideal CVH duration for each of the seven metrics and, altogether, total score; specifically, we presented the minimum, maximum. mean, $25^{th}$, $50^{th}$, $75^{th}$, and $90^{th}$ percentile years separately for participants without CKD and CVD at the baseline. Then, we assessed the correlation between duration of ideal CVH and baseline CVH score based on Spearman's rank correlation.

Each CKD and CVD events were estimated using the Kaplan-Meier method. The hazard ratios (HRs) and 95% confidence intervals (CIs) associated with each ideal CVH duration group were calculated using Cox proportional hazards models with discrete time intervals with ideal CVH duration <5 years group as the reference. The end of the observation period was defined as the date of event, last follow-up, or December 31, 2016, whichever came first. HRs were adjusted for age, sex, education level, and examination site; models evaluating CKD risks additionally adjusted for the baseline eGFR and UACR. Covariates were selected *a priori* on the basis of biological plausibility and previous literature. The proportional hazards assumption was not violated according to graphical inspection of log-minus-log plot and Schoenfeld residuals. Effect modification by cross-categories based on sex and age (i.e., male <50 years, female ≥50 years) was

assessed using multiplicative interaction terms. Secondary analyses examined the association of maintaining individual ideal CVH metrics for 5 years with the risk of developing CKD and CVD alongside their known precursor cardiometabolic diseases, including hypertension, diabetes mellitus, and hypercholesterolemia.

Ten sensitivity analyses were performed. First, we excluded the disease incidence during the first follow-up to account for potential carryover of the risk. Second, we restricted to participants who have attended 4, 5, 6, or all 7 follow-up examinations, separately, to ensure the associations persist regardless of attendance. Conversely, we have conducted additional subgroup analyses on participants who have been followed for less than the median follow-up duration. Third, we assessed the risks assuming no changes in CVH scores for missing examinations, referred to as the *stagnant model*; thus, the most recent previous score would be carried over and be maintained until the subsequent follow-up attendance. Fourth, due to known J-shaped associations of very low body mass index, blood pressure, cholesterol, and fasting glucose levels with CVD risks and all-cause mortality, we further excluded participants with (1) body mass index <18.5 kg/m$^2$; (2) diastolic blood pressure <60 mmHg; (3) low-density lipoprotein cholesterol <25 mg/dL; or (4) fasting glucose <70 mg/dL based on the previous literature.[26-29] Fifth, we employed Fine-Gray modeling[30] to calculate HRs for CKD and CVD events in the presence of a competing risk of CVD, CKD, and cancer, separately. Here, the cumulative incidence function curve is treated as a subdistribution function, which ensures the independent effect of ideal CVH duration on each outcome among participants who had undergone both CKD and

cardiovascular events or/and cancer. Sixth, instead of the stage 3 CKD definition, we examined whether the association persists for eGFR decline by 30% or greater from the baseline level. Seventh, we examined whether maintaining ideal or intermediate CVH is also associated with risk of developing CKD or CVD. Eighth, we examined whether different patterns of CVH category change are associated with significantly different CKD and CVD risks. Specifically, we assessed the risk differences among participants with nearly none, incremental, or early decline to suboptimal (intermediate and poor CVH categories combined) CVH from optimal (ideal) CVH category in reference to participants with persistently suboptimal CVH (Appendix Figure 1). Ninth, we calculated CKD and CVD risks associated with duration of ideal clinical and lifestyle CVH, separately, to compare their relative contributions. Lastly, we modeled the trajectories of clinical CVH scores and assessed whether distinct group membership is associated with significantly different CKD and CVD risks (Appendix Methods).

All statistical tests were two-sided, and statistical significance was set at a *p*-value <0.05. All analyses were performed using R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.4 (SAS Institute Inc., Cary, NC).

# III. Results

## 1. Baseline characteristics

The study included 8,020 participants (median age 50.0 years; 47.9% male), of whom 7,854 without CKD and 7,796 without CVD at baseline. Of the participants, 110 (1.4%) had zero ideal CVH metrics, 497 (6.2%) had one ideal CVH metrics, 1,152 (14.4%) had two ideal CVH metrics, 1,864 (23.2%) had three ideal CVH metrics, 2,018 (25.2%) had four ideal CVH metrics, 1,528 (19.1%) had five ideal CVH metrics, 694 (8.7%) had six ideal CVH metrics, and 157 (2.0%) had seven ideal CVH metrics, respectively (Table 2).

**Table 2. Baseline characteristics of participants according to the number of ideal cardiovascular health metrics**

| | Number of ideal cardiovascular health metrics | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Characteristics | 0<br>n=110 | 1<br>n=497 | 2<br>n=1,152 | 3<br>n=1,864 | 4<br>n=2,018 | 5<br>n=1,528 | 6<br>n=694 | 7<br>n=157 |
| Age, years | 50.06±8.39 | 49.68±7.85 | 51.51±8.43 | 52.57±8.90 | 52.85±8.95 | 51.64±8.88 | 50.20±8.88 | 49.28±8.34 |
| Male sex | 107 (97.27) | 462 (92.96) | 892 (77.43) | 1,097 (58.85) | 812 (40.24) | 361 (23.63) | 96 (13.83) | 16 (10.19) |
| Attained high school degree | 83 (75.45) | 336 (67.61) | 618 (53.65) | 874 (46.89) | 779 (38.60) | 603 (39.46) | 303 (43.66) | 73 (46.50) |
| Body mass index, kg/m$^2$ | 26.52±2.46 | 26.22±2.40 | 25.68±2.72 | 25.19±2.95 | 24.63±3.23 | 23.80±3.10 | 22.39±2.58 | 21.12±1.52 |
| Triglyceride, mg/dL | 269.74±194.54 | 219.32±148.91 | 192.97±137.96 | 164.55±112.38 | 138.31±79.29 | 121.46±73.30 | 104.69±63.56 | 94.83±44.60 |
| HDL-cholesterol, mg/dL | 45.75±7.96 | 46.52±9.85 | 47.64±11.36 | 49.21±12.14 | 49.91±11.89 | 50.24±11.84 | 52.01±11.42 | 51.55±10.63 |
| eGFR, ml/min/1.73m$^2$ | 88.07±14.86 | 88.89±14.85 | 90.05±15.09 | 91.67±15.26 | 93.82±15.35 | 96.04±15.20 | 98.06±13.95 | 99.81±14.35 |
| Cigarette smoking status | | | | | | | | |
| Never smoker | 0 (0.0) | 31 (6.24) | 294 (25.52) | 911 (48.87) | 1,389 (68.83) | 1,285 (84.10) | 655 (94.38) | 157 (100.0) |
| Former smoker | 52 (47.27) | 193 (38.83) | 356 (30.90) | 368 (19.74) | 236 (11.69) | 71 (4.65) | 8 (1.15) | 0 (0.0) |
| Current smoker | 58 (52.73) | 273 (54.93) | 502 (43.58) | 585 (31.38) | 393 (19.47) | 172 (11.26) | 31 (4.47) | 0 (0.0) |
| Alcohol drinking status | | | | | | | | |
| Non-drinker | 0 (0.0) | 10 (2.01) | 143 (12.41) | 583 (31.28) | 1,050 (52.03) | 1,096 (71.73) | 609 (87.75) | 157 (100.0) |
| Former drinker | 13 (11.82) | 40 (8.05) | 133 (11.55) | 145 (7.78) | 106 (5.25) | 52 (3.40) | 6 (0.86) | 0 (0.0) |
| Current drinker | 97 (88.18) | 447 (89.94) | 876 (76.04) | 1,136 (60.94) | 862 (42.72) | 380 (24.87) | 79 (11.38) | 0 (0.0) |
| Physical activity | | | | | | | | |
| 75+ min of vigorous or 150+ min of moderate activity | 0 (0.0) | 112 (22.54) | 498 (43.23) | 1,017 (54.56) | 1,333 (66.06) | 1,090 (71.34) | 545 (78.53) | 157 (100.0) |
| More than 0 min but less than the recommendation | 26 (23.64) | 86 (17.30) | 165 (14.32) | 177 (9.50) | 145 (7.19) | 82 (5.37) | 35 (5.04) | 0 (0.0) |
| 0 minutes | 84 (76.36) | 299 (60.16) | 489 (42.45) | 670 (35.94) | 540 (26.76) | 356 (23.30) | 114 (16.43) | 0 (0.0) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Body mass index, kg/m$^2$ | | | | | | | | |
| <23 | 0 (0.0) | 16 (3.22) | 139 (12.07) | 379 (20.33) | 602 (29.83) | 665 (43.52) | 498 (71.76) | 157 (100.0) |
| 23-24.9 | 34 (30.91) | 153 (30.78) | 341 (29.60) | 542 (29.08) | 567 (28.10) | 368 (24.08) | 105 (15.13) | 0 (0.0) |
| ≥25 | 76 (69.09) | 328 (66.00) | 672 (58.33) | 943 (50.59) | 849 (42.07) | 495 (32.40) | 91 (13.11) | 0 (0.0) |
| Total cholesterol, mg/dL | | | | | | | | |
| <200 (Untreated) | 0 (0.0) | 51 (10.26) | 292 (25.35) | 802 (43.03) | 1,131 (56.05) | 1,168 (76.44) | 632 (91.07) | 157 (100.0) |
| 200-239 or treated to ideal | 62 (56.36) | 308 (61.97) | 594 (51.56) | 722 (38.73) | 671 (33.25) | 287 (18.78) | 54 (7.78) | 0 (0.0) |
| ≥240 | 48 (43.64) | 138 (27.77) | 266 (23.09) | 340 (18.24) | 216 (10.70) | 73 (4.78) | 8 (1.15) | 0 (0.0) |
| Blood pressure, mmHg | | | | | | | | |
| <120/80 (Untreated) | 0 (0.0) | 33 (6.64) | 159 (13.80) | 375 (20.12) | 693 (34.34) | 852 (55.76) | 540 (77.81) | 157 (100.0) |
| SBP 120-139 or DBP <90 or treated to ideal | 60 (54.55) | 312 (62.78) | 663 (57.55) | 1,025 (54.99) | 880 (43.61) | 468 (30.63) | 111 (15.99) | 0 (0.0) |
| SBP ≥140 or DBP ≥90 | 50 (45.45) | 152 (30.58) | 330 (28.65) | 464 (24.89) | 445 (22.05) | 208 (13.6) | 43 (6.20) | 0 (0.0) |
| Fasting glucose, mg/dL | | | | | | | | |
| <100 (Untreated) | 0 (0.0) | 244 (49.09) | 779 (67.62) | 1,525 (81.81) | 1,874 (92.86) | 1,484 (97.12) | 685 (98.70) | 157 (100.0) |
| 100-125 or treated to ideal | 77 (70.00) | 184 (37.02) | 270 (23.44) | 253 (13.57) | 104 (5.15) | 33 (2.16) | 4 (0.58) | 0 (0.0) |
| ≥126 | 33 (30.00) | 69 (13.88) | 103 (8.94) | 86 (4.61) | 40 (1.98) | 11 (0.72) | 5 (0.72) | 0 (0.0) |

*Values are presented as mean±standard deviation or number (%).
Abbreviations: DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein

Participants with greater number of ideal CVH metrics at baseline were distinguishably of female sex. Indeed, the distribution of CVH scores of female participants was skewed more to left than that of the male (Appendix Table 1, Figures 4A&B). Interestingly, there were no defined age nor education attainment trends across the number of baseline ideal CVH metrics. Naturally, higher proportion of participants with greater number of ideal CVH metrics satisfied more guidelines-recommended anthropometry, glycemic and lipid profiles, and lifestyle. Compared to 818 CKD- and CVD-free participants excluded in the analyses due to missing CVH score, the included participants had lower prevalence of diabetes mellitus (4.4% vs. 6.4%) and higher eGFR (93.3 ml/min/1.73m$^2$ vs. 91.8 ml/min/1.73m$^2$), but were otherwise demographically comparable (Appendix Table 2).

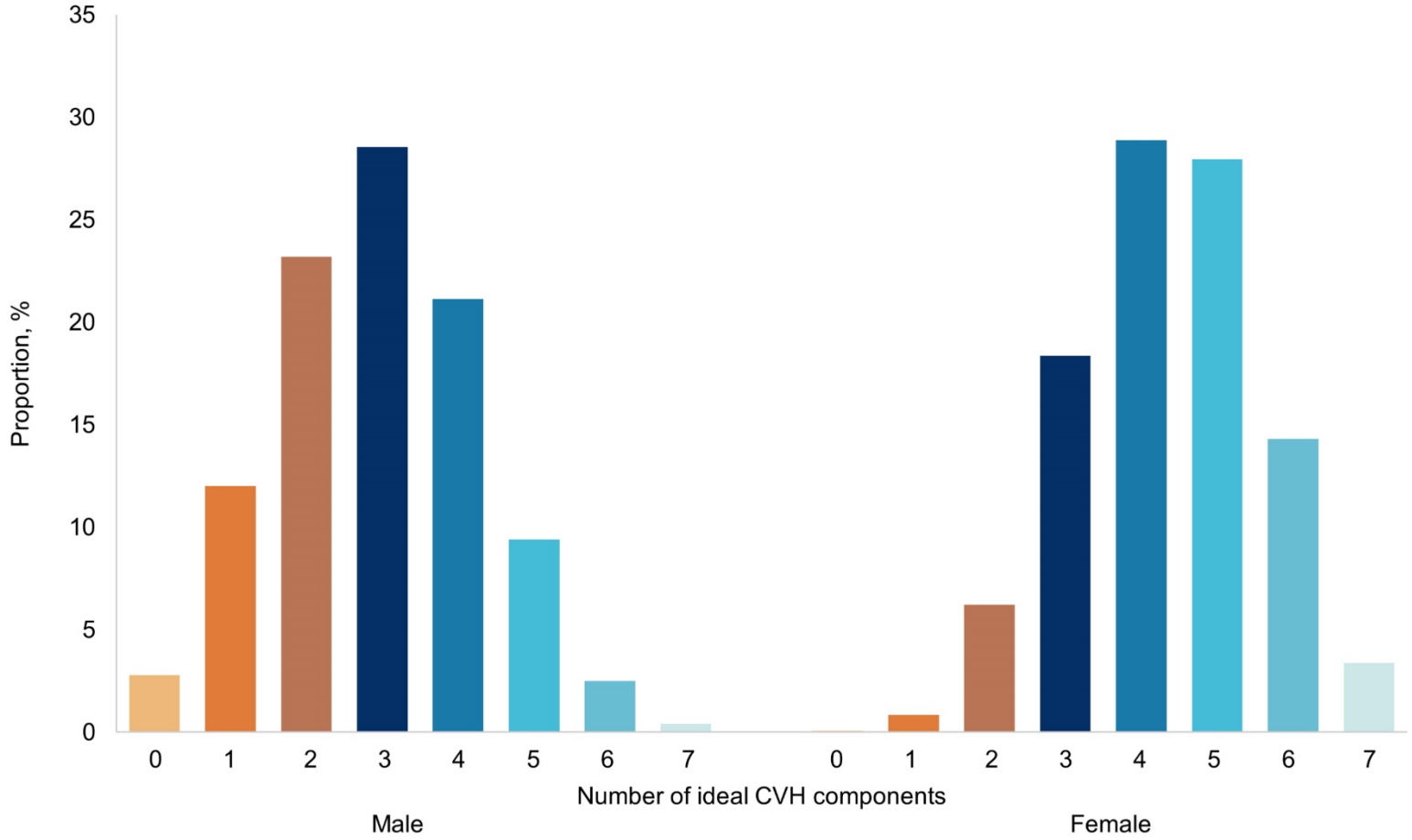


**Figure 4A. Distribution of baseline number of ideal cardiovascular health (CVH) components by sex**

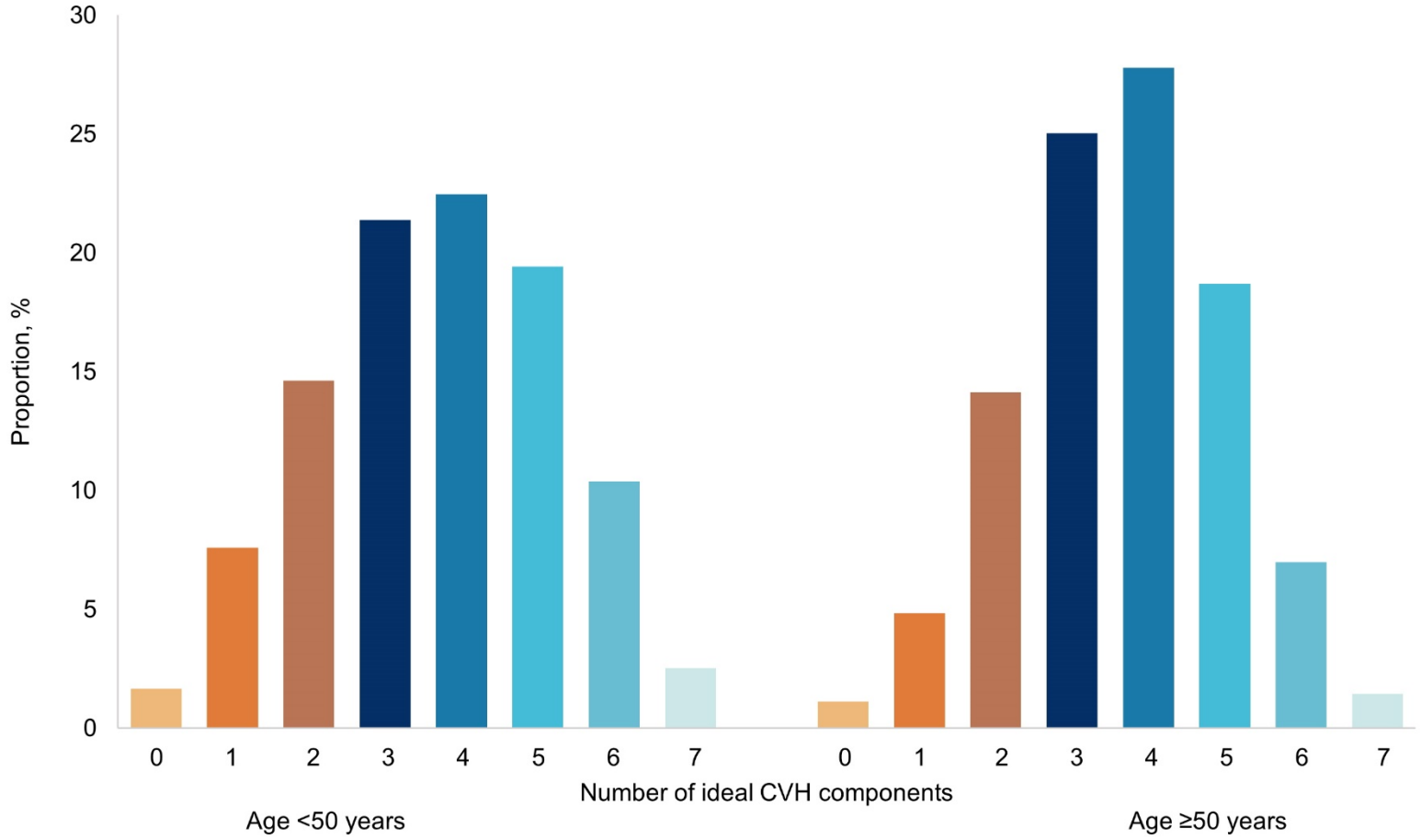


**Figure 4B. Distribution of baseline number of ideal cardiovascular health (CVH) components by median age**

Over median follow-up of 15.0 years, 7,156 (89.2%) participants had less than 5 years of ideal CVH, 525 (6.5%) had 5 to 10 years of ideal CVH, and 339 (2.1%) had 10 or greater years of ideal CVH, respectively (Table 3). At baseline, those who maintained ideal CVH 10 years or longer were more likely to be female, to attain high school degree, be non-smoker, be non-drinker, and less likely to have metabolic abnormalities in comparison with the shorter duration ideal CVH groups.

**Table 3. Baseline characteristics of study participants at baseline by duration lived in ideal cardiovascular health**

| Characteristic | Duration of ideal CVH, No. (%) of participants | | |
|---|---|---|---|
| | ≥10 years (n=339) | 5-10 years (n=525) | <5 years (n=7,156) |
| Age, year | 48.38±8.13 | 48.60±7.93 | 52.23±8.83 |
| Male sex | 51 (15.04) | 82 (15.62) | 3,710 (51.84) |
| Attained high school degree | 192 (56.64) | 268 (51.05) | 3,209 (44.84) |
| BMI, kg/m$^2$ | 21.75±2.06 | 22.54±2.19 | 24.90±3.11 |
| Current smoker | 9 (2.65) | 20 (3.81) | 1,985 (27.74) |
| Current drinker | 38 (11.21) | 100 (19.05) | 3,739 (52.25) |
| MVPA 150+ min/week | 181 (53.39) | 331 (63.05) | 4,240 (59.25) |
| Systolic blood pressure, mm Hg | 107.03±13.25 | 109.81±13.45 | 123.22±18.51 |
| Diastolic blood pressure, mm Hg | 70.82±9.14 | 73.04±9.57 | 81.66±11.57 |
| Hypertension | 16 (4.72) | 42 (8.00) | 2,676 (37.40) |
| Total cholesterol, mg/dL | 179.95±27.25 | 183.31±29.58 | 201.29±36.46 |
| HDL cholesterol, mg/dL | 53.31±11.64 | 51.90±11.31 | 49.07±11.70 |
| Fasting glucose level, mg/dL | 84.50±8.20 | 86.03±15.20 | 93.13±22.94 |
| Diabetes mellitus | 2 (0.59) | 7 (1.33) | 347 (4.85) |
| eGFR, ml/min/1.73m$^2$ | 98.66±15.13 | 97.90±15.04 | 92.71±15.27 |
| Chronic kidney disease | 3 (0.88) | 7 (1.33) | 156 (2.18) |
| Cardiovascular disease | 5 (1.47) | 2 (0.38) | 217 (3.03) |
| Coronary artery disease | 2 (0.59) | 1 (0.19) | 125 (1.75) |
| Cerebrovascular disease | 4 (1.18) | 1 (0.19) | 86 (1.20) |
| Heart failure | 0 (0.0) | 0 (0.0) | 18 (0.25) |
| CVH score | 11.98±1.58 | 11.63±1.56 | 8.43±2.33 |
| CVH score category | | | |
| Ideal (12-14) | 234 (69.03) | 330 (62.86) | 573 (8.01) |
| Intermediate (8-11) | 104 (30.68) | 185 (35.24) | 4,182 (58.44) |
| Poor (0-7) | 1 (0.29) | 10 (1.90) | 2,401 (33.55) |

*Values are presented as mean±standard deviation or number (%).

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; CVH, cardiovascular health; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; MVPA, moderate-vigorous physical activity

## 2. Duration of ideal CVH

Table 4 illustrates proportional distribution of the duration of each ideal CVH metrics and total score. Regardless of CKD or CVD prevalence at baseline, high body mass index largely contributed to low CVH score, followed by high blood pressure and low physical activity engagement. In contrast, considerable proportion of participants lived with ideal fasting glucose level and never-smoking status (Appendix Table 3).

In general, the duration of ideal CVH was moderately correlated with baseline CVH score (r, 0.61; $p$ <0.001). The correlations among individual baseline CVH metrics score with their respective ideal duration were moderately-to-highly positive, except for physical activity (Appendix Table 4).

**Table 4. Proportional distribution of the duration of each ideal cardiovascular health metric and total score**

| | Percentile | | | | |
|---|---|---|---|---|---|
| Metric | 0-19th | 20-39th | 40-59th | 60-79th | 80-100th |
| Without CKD at baseline (n=7,854) | | | | | |
| Ideal CVH score | 84.29 | 7.50 | 2.93 | 3.08 | 2.20 |
| Ideal cigarette smoking | 36.94 | 2.69 | 1.39 | 2.56 | 56.43 |
| Ideal physical activity | 46.93 | 22.40 | 9.74 | 12.17 | 8.76 |
| Ideal alcohol drinking | 44.68 | 7.30 | 4.85 | 10.47 | 32.71 |
| Ideal body mass index | 61.24 | 6.37 | 3.86 | 6.07 | 22.46 |
| Ideal blood pressure | 50.32 | 12.26 | 7.36 | 13.32 | 16.74 |
| Ideal fasting glucose | 14.37 | 8.19 | 6.26 | 16.18 | 54.99 |
| Ideal total cholesterol | 27.41 | 15.66 | 9.40 | 18.00 | 29.53 |
| Without CVD at baseline (n=7,796) | | | | | |
| Ideal CVH score | 84.17 | 7.56 | 2.96 | 3.12 | 2.19 |
| Ideal cigarette smoking | 36.75 | 2.68 | 1.36 | 2.50 | 56.71 |
| Ideal physical activity | 46.92 | 22.59 | 9.68 | 12.10 | 8.71 |
| Ideal alcohol drinking | 44.41 | 7.36 | 4.93 | 10.51 | 32.80 |
| Ideal body mass index | 61.07 | 6.45 | 3.93 | 6.12 | 22.43 |
| Ideal blood pressure | 50.33 | 12.31 | 7.36 | 13.29 | 16.70 |
| Ideal fasting glucose | 14.32 | 8.15 | 6.18 | 16.20 | 55.16 |
| Ideal total cholesterol | 27.45 | 15.69 | 9.27 | 18.11 | 29.48 |

*The unit is in percentage.

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; CVH, cardiovascular health

### 3. Outcomes incidence

During a median follow-up of 15.0 ($25^{th}$-$75^{th}$ percentile, 14.2-15.6; minimum-maximum, 1.6-15.6) years, 1,401 new CKD events occurred. Age- and sex-adjusted CKD incidence largely varied by the number of clinical and lifestyle CVH metrics (Figure 5A). Age- and sex-adjusted CKD incidence rates per 1,000 person-years were 30.1 among participants with zero versus 10.6 with seven ideal CVH metrics at baseline.

During a median follow-up of 15.1 ($25^{th}$-$75^{th}$ percentile, 14.3-15.6; minimum-maximum, 1.7-15.6) years, 493 new CVD events occurred. Likewise, age- and sex-adjusted CKD incidence rates ranged by the combination of clinical and lifestyle CVH metrics (Figure 5B). Age- and sex-adjusted CVD incidence rates per 1,000 person-years were 6.5 among participants with zero versus 2.7 with seven ideal CVH metrics at baseline.

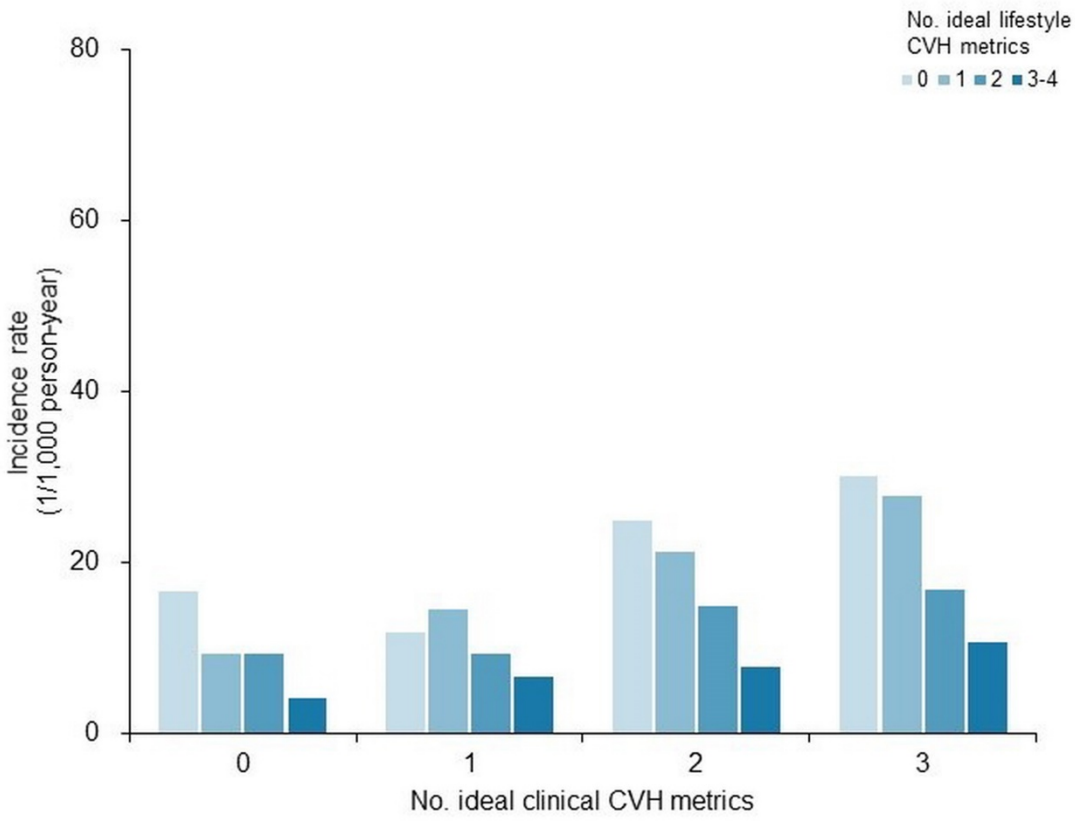


**Figure 5A. Age- and sex-adjusted chronic kidney disease incidence by baseline number of ideal cardiovascular health (CVH) metrics**

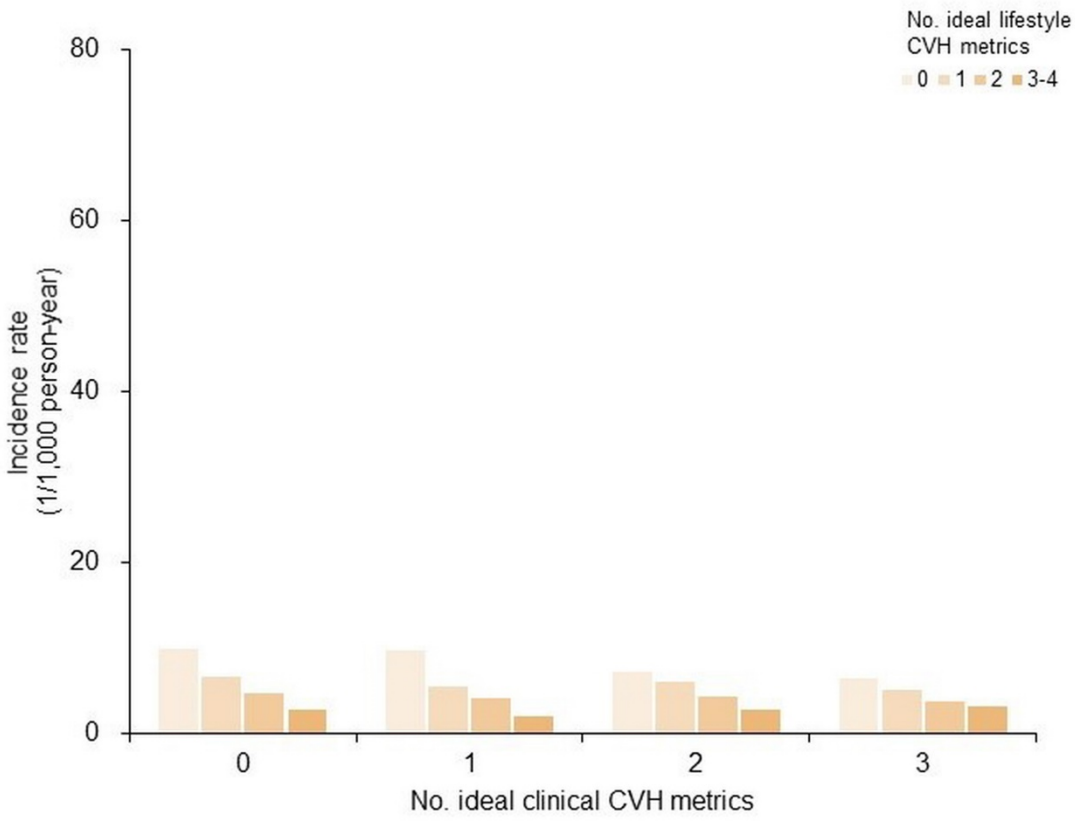


**Figure 5B. Age- and sex-adjusted cardiovascular disease incidence by baseline number of ideal cardiovascular health (CVH) metrics**

**4. Primary analyses**

Table 5 and Figure 6 illustrate the disease event rates and risks associated with duration of ideal CVH. There were negatively graded CKD event rates by the duration lived in ideal CVH (less than 5 years, 19.0%; 5 to 10 years, 9.5%; ≥10 years, 6.9%). In fully adjusted Cox model, 5 to 10 (HR, 0.63 [95% CI, 0.39-0.93]) and ≥10 years (HR, 0.33 [95% CI, 0.15-0.74]) lived with ideal CVH were each associated with a lower risk for CKD in reference to the <5 years group (*P* trend, 0.0057).

The CVD event rates were the highest among participants lived with less than 5 years of ideal CVH (6.7%), followed by those lived with 5 to 10 years (4.4%) and ≥10 years (1.2%), respectively. In reference to the <5 years group, participants lived with 5 to 10 years of ideal CVH had lower CVD risk (HR, 0.83 [95% CI, 0.54-1.27]) yet without statistical significance. However, living with ideal CVH for ≥10 years was associated with significantly lower CVD risk (HR, 0.22 [95% CI, 0.08-0.60]).

**Table 5. Association of maintaining ideal cardiovascular health with risk of developing chronic kidney disease or cardiovascular disease on follow-up**

| Outcome | Ideal CVH Duration | No. of Events/No. at Risk (%) | HR (95% CI) | *P* trend |
|---|---|---|---|---|
| †Chronic kidney disease | <5 years | 1,329/7,000 (18.99) | 1.00 Reference | |
| | 5 to 10 years | 49/518 (9.46) | 0.63 (0.39-0.93) | 0.0057 |
| | ≥10 years | 23/336 (6.85) | 0.33 (0.15-0.74) | |
| ‡Cardiovascular disease | <5 years | 466/6,939 (6.72) | 1.00 Reference | |
| | 5 to 10 years | 23/523 (4.40) | 0.83 (0.54-1.27) | 0.0087 |
| | ≥10 years | 4/334 (1.20) | 0.22 (0.08-0.60) | |
| Coronary artery disease | <5 years | 266/6,939 (3.83) | 1.00 Reference | |
| | 5 to 10 years | 7/523 (1.34) | 0.42 (0.20-0.89) | 0.0239 |
| | ≥10 years | 2/334 (0.60) | 0.19 (0.05-0.75) | |
| Cerebrovascular disease | <5 years | 210/6,939 (3.03) | 1.00 Reference | |
| | 5 to 10 years | 16/523 (3.06) | 1.43 (0.85-2.41) | 0.0514 |
| | ≥10 years | 2/334 (0.60) | 0.28 (0.07-1.12) | |
| Heart failure | <5 years | 9/6,939 (0.13) | 1.00 Reference | |
| | 5 to 10 years | 1/523 (0.19) | 1.24 (0.15-10.29) | 0.8429 |
| | ≥10 years | 0/334 (0.0) | N/A | |

*All models adjusted for age, sex, education level, and examination site.

†Additionally adjusted for baseline estimated glomerular filtration rate and urine albumin-to-creatinine ratio.

‡First cardiovascular disease event: coronary artery disease, cerebrovascular disease, or heart failure

Abbreviations: CI, confidence interval; CVH, cardiovascular health; HR, hazard ratio

| Outcome | Ideal CVH Duration | No. of Events/ No. at Risk (%) | HR (95% CI) | *P* Trend |
|---|---|---|---|---|
| Chronic kidney disease | <5 years | 1,329/7,000 (18.99) | 1.00 Reference | 0.0057 |
| | 5 to 10 years | 49/518 (9.46) | 0.63 (0.39-0.93) | |
| | ≥10 years | 23/336 (6.85) | 0.33 (0.15-0.74) | |
| Cardiovascular disease | <5 years | 466/6,939 (6.72) | 1.00 Reference | 0.0087 |
| | 5 to 10 years | 23/523 (4.40) | 0.83 (0.54-1.27) | |
| | ≥10 years | 4/334 (1.20) | 0.22 (0.08-0.60) | |
| Coronary artery disease | <5 years | 266/6,939 (3.83) | 1.00 Reference | 0.0239 |
| | 5 to 10 years | 7/523 (1.34) | 0.42 (0.20-0.89) | |
| | ≥10 years | 2/334 (0.60) | 0.19 (0.05-0.75) | |
| Cerebrovascular disease | <5 years | 210/6,939 (3.03) | 1.00 Reference | 0.0514 |
| | 5 to 10 years | 16/523 (3.06) | 1.43 (0.85-2.41) | |
| | ≥10 years | 2/334 (0.60) | 0.28 (0.07-1.12) | |
| Heart failure | <5 years | 9/6,939 (0.13) | 1.00 Reference | 0.8429 |
| | 5 to 10 years | 1/523 (0.19) | 1.24 (0.15-10.29) | |
| | ≥10 years | 0/334 (0.0) | N/A | |

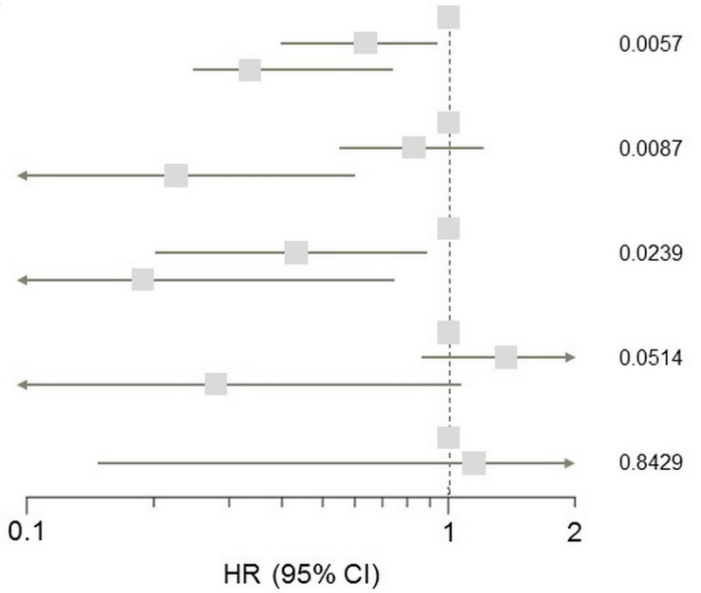


**Figure 6. Forest plot of the association of ideal cardiovascular health (CVH) duration with risk of chronic kidney disease and cardiovascular disease on follow-up**

When we reexamined the risks by CVD subtypes, longer ideal CVH duration was associated with significantly lower risk for coronary artery disease (5 to 10 years: HR, 0.42 [95% CI, 0.20-0.89], ≥10 years: HR, 0.19 [95% CI, 0.05-0.75]) and marginally lower risk for cerebrovascular disease (*P* trend, 0.0514). Due to a very small number of cases, no association was observed for heart failure.

No significant effect measure modification by sex and age group was observed for the associations of ideal CVH duration with either CKD or CVD outcomes.

**5. Secondary analyses**

To explore the individual clinical and lifestyle contribution, we examined the association of maintaining individual ideal CVH components for ≥5 years with the risk of developing CKD and CVD alongside their established precursors—hypertension, diabetes mellitus, and hypercholesterolemia (Appendix Figures 2-4, Table 6). Overall, maintaining ideal clinical CVH metrics for ≥5 years was consistently associated with lowered risk for all outcomes in reference to less than 5 years of maintenance. A notable exception was total cholesterol, which, alone, demonstrated no lowered effect on CKD (HR, 0.94 [95% CI, 0.79-1.13]) nor CVD (HR, 1.01 [95% CI, 0.84-1.22]) risks. Individual lifestyle metrics were associated with bidirectional yet mostly statistically insignificant risks for each outcome.

**Table 6. Association of maintaining ideal cardiovascular health components for 5 years or longer with risk of developing hypertension, diabetes mellitus, hypercholesterolemia, chronic kidney disease, or cardiovascular disease on follow-up**

| Outcome | No. of Events/No. at Risk (%) | HR (95% CI) | *p*-value |
|---|---|---|---|
| Hypertension† | | | |
| Cigarette smoking | 2,072/5,286 (39.20) | 1.00 (0.87-1.15) | 0.9889 |
| Physical activity | | 0.96 (0.88-1.05) | 0.3435 |
| Alcohol drinking | | 0.96 (0.87-1.07) | 0.4824 |
| Body mass index | | 0.67 (0.61-0.73) | <0.0001 |
| Blood pressure | | 0.16 (0.14-0.18) | <0.0001 |
| Fasting glucose | | 0.87 (0.77-0.97) | 0.0121 |
| Total cholesterol | | 0.98 (0.89-1.07) | 0.6327 |
| Diabetes mellitus‡ | | | |
| Cigarette smoking | 796/7,664 (10.39) | 0.88 (0.71-1.08) | 0.2133 |
| Physical activity | | 1.00 (0.86-1.15) | 0.9713 |
| Alcohol drinking | | 1.07 (0.90-1.28) | 0.4326 |
| Body mass index | | 0.54 (0.46-0.65) | <0.0001 |
| Blood pressure | | 0.57 (0.48-0.68) | <0.0001 |
| Fasting glucose | | 0.13 (0.11-0.16) | <0.0001 |
| Total cholesterol | | 1.04 (0.90-1.20) | 0.6059 |
| Hypercholesterolemia§ | | | |
| Cigarette smoking | 1,902/6,919 (27.49) | 1.07 (0.92-1.25) | 0.3750 |
| Physical activity | | 1.05 (0.95-1.15) | 0.3346 |
| Alcohol drinking | | 1.24 (1.11-1.39) | 0.0001 |
| Body mass index | | 0.83 (0.75-0.91) | 0.0001 |
| Blood pressure | | 0.78 (0.71-0.86) | <0.0001 |
| Fasting glucose | | 0.89 (0.79-0.99) | 0.0455 |
| Total cholesterol | | 0.28 (0.25-0.31) | <0.0001 |
| Chronic kidney disease‖ | | | |
| Cigarette smoking | 1,401/7,854 (17.84) | 1.04 (0.78-1.39) | 0.7995 |
| Physical activity | | 1.29 (1.07-1.56) | 0.0069 |
| Alcohol drinking | | 1.12 (0.89-1.42) | 0.3433 |
| Body mass index | | 0.73 (0.60-0.89) | 0.0021 |
| Blood pressure | | 0.72 (0.59-0.88) | 0.0016 |
| Fasting glucose | | 0.73 (0.59-0.90) | 0.0037 |
| Total cholesterol | | 0.94 (0.79-1.13) | 0.5304 |
| Cardiovascular disease¶ | | | |
| Cigarette smoking | 493/7,796 (6.32) | 0.79 (0.60-1.03) | 0.0835 |
| Physical activity | | 1.02 (0.84-1.22) | 0.8730 |
| Alcohol drinking | | 1.25 (1.00-1.56) | 0.0490 |
| Body mass index | | 0.66 (0.54-0.80) | <0.0001 |
| Blood pressure | | 0.59 (0.48-0.72) | <0.0001 |
| Fasting glucose | | 0.70 (0.57-0.86) | 0.0007 |
| Total cholesterol | | 1.01 (0.84-1.22) | 0.9218 |

The HRs are in reference to participants with less than 5 years of ideal CVH components.

*All models are adjusted for age, sex, education level, and examination site.

†Additionally adjusted for baseline SBP and DBP

‡Additionally adjusted for baseline fasting blood glucose
§Additionally adjusted for baseline total cholesterol
ǀModels are additionally adjusted for baseline estimated glomerular filtration rate and urine albumin-to-creatinine ratio.
¶First cardiovascular disease event: coronary artery disease, cerebrovascular disease, or heart failure
Abbreviations: CI, confidence interval; CKD, chronic kidney disease; CVH, cardiovascular-health; DBP, diastolic blood pressure; HR, hazard ratio; SBP, systolic blood pressure

**6. Sensitivity Analyses**

We excluded the events from the first follow-up to account for potential carry-over. Regardless, longer ideal CVH duration remained negatively associated with risks of CKD (*P* trend, 0.0071) and CVD—specifically coronary artery disease (*P* trend, 0.0181) (Appendix Table 5). In subgroup analyses restricted to participants with high follow-up attendance, the associations were attenuated yet remained significant (Appendix Tables 6-8). However, among participants who have attended all seven follow-up examinations, longer ideal CVH duration was marginally associated with lower CKD risk (*P* trend, 0.0517) yet diminished for CVD (*P* trend, 0.1199) (Appendix Table 9). Because a short follow-up duration may limit potential for event occurrence, we have also restricted the analyses to participants who have been followed less than the median duration; the associations remained robust (Appendix Table 10).

We also assessed CKD and CVD risks based on the *stagnant model*, which carries over the last follow-up CVH score for missing examinations. Despite moderate left-skewing of the CVH scores, no significant changes in the associations were observed (Appendix Table 11). To prevent potential dilution of the results from participants with adversely low clinical CVH profile, we restricted the analyses to participants within normal or high clinical CVH metrics range. Notwithstanding minutely blunted risk gradation, no visible changes were observed. (Appendix Table 12). As a modest proportion of the participants underwent both CKD and CVD during follow-up, we estimated the cumulative

incidence function semiparametrically to regard competing risks from each other (Appendix Table 13). This affected the results minimally. Likewise, the associations were unaffected when treating cancer as a competing risk.

When substituting the eGFR <60 ml/min/1.73m$^2$ outcome definition with 30% or greater decline from the baseline value, the results were similar. In reference to the ideal CVH duration <5 years group, participants maintaining ideal CVH duration 5 to 10 years (HR, 0.87 [95% CI, 0.76-1.05]) or ≥10 years (HR, 0.66 [95% CI, 0.49-0.88]) had lowered risk for adverse renal outcome (Appendix Table 14).

We further expanded the analyses to more lenient definition of favorable CVH. Maintaining ideal or intermediate CVH displayed diminishingly graded risks for all outcomes (Appendix Table 15, Appendix Figure 5). Notably, in reference to the <5 years group, those maintaining ideal or intermediate CVH for ≥10 years had significantly lowered risk for composite (HR, 0.61 [95% CI, 0.49-0.75]) and all subtypes of CVD, including coronary artery disease**,** (HR, 0.74 [95% CI, 0.61-0.97]), cerebrovascular disease, (HR, 0.53 [95% CI, 0.39-0.72]), and heart failure, (HR, 0.11 [95% CI, 0.02-0.58]). However, maintaining ideal or intermediate CVH for 5 to 10 years was not significantly associated with lowered risks for CKD and CVD.

As a proxy to duration, we explored whether different rates at which optimal (ideal) CVH deteriorates to suboptimal (intermediate or poor) CVH is also meaningfully associated with the outcomes (Appendix Table 16). Compared to participants who remained in suboptimal CVH for (near-)entirety, those who

gradually declined to suboptimal CVH category had lower risks for CKD (HR, 0.69 [95% CI, 0.54-0.81]) and CVD (HR, 0.65 [0.51-0.79]). The risks were exceptionally lower among participants with consistently optimal CVH (CKD: HR, 0.43 [95% CI, 0.12-0.80], CVD: HR, 0.38 [95% CI, 0.07-0.85]).

Furthermore, we calculated the duration of ideal clinical and lifestyle CVH metrics, separately, to compare their relative utility (Appendix Tables 17, 18). Overall, the associations were consistently robust based on clinical CVH metrics yet partly attributed by lifestyle factors. For instance, maintaining even 5 to 10 years of ideal clinical (HR, 0.72 [95% CI 0.61-0.85]) and lifestyle (HR, 0.83 [95% CI 0.70-0.98]) CVH were independently associated with lowered CKD risk. However, maintaining 5 to 10 years of ideal lifestyle CVH, alone, did not explain significantly different CVD risk (HR, 0.98 [95% CI, 0.84-1.28]).

Lastly, we delineated clinical CVH score trajectories among a subset of participants who had attended at least two follow-up examinations (Appendix Figure 6). We identified 5 distinct trajectories, including low-stagnant group (n=979 [13.7%]), intermediate-early decline group (n=2,000 [28.0%]), intermediate-stagnant group (n=2,086 [29.2%]), high-stagnant group (n=1,486 [20.8%]), and optimal-late decline group (n=593 [8.3%]). Overall, all five groups maintained the baseline clinical CVH score across the follow-ups without much fluctuations. The clinical CVH score trajectory group membership was associated with both CKD (Appendix Table 19) and CVD (Appendix Table 20), displaying dose-response-like risks. In reference to the low-stagnant group, the HRs and 95% CIs for CKD are as follows: intermediate-early decline, 0.75 [0.64-0.84];

intermediate-stagnant, 0.69 [0.57-0.79]; high-stagnant, 0.62 [0.51-0.77]; optimal-late decline, 0.41 [0.17-0.72]. Additional adjustment for baseline CVH score attenuated the risks yet yielded similar results. Likewise, in reference to the low-stagnant group, the HRs and 95% CIs for CVD exhibited graded lowered risks: intermediate-early decline, 0.72 [0.55-0.92]; intermediate-stagnant, 0.65 [0.29-0.87]; high-stagnant, 0.51 [0.11-0.89]; optimal-late decline, 0.29 [0.01-0.77].

# IV. Discussion

In this study of middle-aged Korean adults, longer duration of ideal CVH was associated with incrementally lowered risks for CKD and CVD over a median follow-up of 15.0 years. The associations were independent of age, sex, socioeconomic status, baseline health, and frequency/duration of follow-up. As the universal National Health Insurance Service[31] provides general health examinations to all Korean adults every 1 to 2 years (similar to this study's follow-up interval), the CVH score may be regularly calculated and easily tracked. In this context, our findings establish the potency of comprehensive clinical and lifestyle CVH metrics that may be incorporated into clinical guidelines and public health policies in devising long-term cardiometabolic health management.

Our findings are consistent with previous literature that assessed the impact of the American Heart Association's version of the CVH score on subclinical and hard cardiovascular outcomes. In the Framingham Offspring Study (mean age 55.4 years; 45.3% male), worsening temporal trends of ideal CVH over 20 years were associated with increased adverse echocardiographic atherosclerotic measures.[32] Similarly in a Korean hospital-based cohort of low-risk adults (mean age 41.3 years; 78.7% male), higher baseline CVH score was negatively associated with coronary artery calcium development and progression.[14] The maintenance of ideal CVH in midlife extends to favorable cardiovascular structure and function in late life. Compared to participants who had undergone ≥0.5 point/decade CVH score increase, the counterparts with >1

point/decade decrease exhibited worse left ventricular structure (left ventricular hypertrophy, 9.2% vs. 5.7%; *P* trend, 0.008), arterial function (mean arterial pressure, 91 mmHg vs. 85 mmHg; *P* trend, <0.001), and myocardial stress (high-sensitivity troponin T, 10.3 ng/L vs. 8.9 ng/L; *P* trend <0.001).[33] The benefits of sustained ideal CVH are also projected to all CVD subtypes, regardless of age, sex, race, and underlying metabolic disorders.[33,34] However, the aforementioned studies had a number of differences compared with the present analysis: (1) the participants were predominantly white/black race;[32,33] (2) a considerable proportion already had atherosclerotic lesion;[14] (3) cardiovascular outcomes were assessed in late life;[32] (4) the cohort was composed largely of participants with prediabetes/diabetes;[33] and (5) a single or very few CVH score(s) were considered with limited follow-up duration.[14,32] Considering the varying distributions of each CVH components across sociodemographics,[35] the current study advances the prior work by demonstrating that long-term CVH is associated with CVD and its preceding target organ damage in a low-risk, community-dwelling population.

To consider cumulative CVH, the Framingham Offspring Study team has investigated the duration of fair CVH on cardiometabolic outcomes. Among 1,445 participants (mean age 60 years, 48% male), each 5-year duration with intermediate or ideal CVH was associated with lowered HRs [95% CIs] for CKD (0.75 [0.63-0.89]) and CVD (0.73 [0.63-0.85]) over a median follow-up of 16 years[36]—which were analogous to our supplementary analyses of combined ideal and intermediate categories (Appendix Table 12). However, several differences should be noted. First, our study substituted the traditional Life Simple 7's diet

score with alcohol drinking, as (1) a nationwide study[37] has reported age-varying rate of excessive alcohol consumption; whereas (2) the proportion of Korean adults with healthy diet by the Life's Simple 7 criteria was very low (overall 1.3%) regardless of CVH score.[14] Furthermore, our primary analyses quantified the benefits of strictly ideal CVH duration, as our participants had significantly lower prevalence of hypertension (37% vs. 67%), diabetes mellitus (5% vs. 21%), and level of total cholesterol (201 mg/dL vs. 208 mg/dL) than the Framingham Offspring cohort[36] even in the shortest ideal CVH duration category (<5 years). Our results warrant promising cardiovascular outcomes in general population with only mildly adverse risk levels. Methodological differences should also be noted. The aforementioned study[36] calculated the ideal duration as the number of examination cycles with available CVH score multiplied by the mean interval (4 years) between follow-ups, whereas we summed the exact years between each follow-up (if present for all) or assumed linear changes between the anteceding and succeeding follow-ups (for participants with imperfect attendance). However, it remains to be determined whether the deterioration or improvements in cardiometabolic profile can best be assessed assuming linearity.

Nonetheless, our results illustrate how critical comprehensive lifestyle modification and pharmacological interventions in midlife are. Indeed, the absence of established risk factors at 50 years of age (equivalent to our study median) was associated with very low lifetime CVD risk, longer survival, and improved physical, mental, and social functioning in older age.[17,38] Beyond, prolongation of ideal CVH is also essential. Whereas maintaining ideal CVH for 5

years or longer were associated with lowered CKD risk (main analysis), a brief maintenance was not meaningful (Appendix Table 21). Moreover, as extensive evidence has been amassed stressing the importance of achieving normal range body mass index,[39] blood pressure,[40] blood glucose,[41] and cholesterol[42] even in young adulthood, public health programs should aim to prevent development of risk factors earlier on and to aid favorable CVH sustenance.

Furthermore, our separate analyses of each clinical and lifestyle CVH duration illustrated the utility of all anthropometric, blood test, and health behavior measures. Here, the maintenance of clinical CVH metrics demonstrated relatively superior contribution in CKD and CVD risk assessment compared to that of the lifestyle CVH. However, as clinical presentations are largely shaped by lifestyle factors (and vice versa),[43] we witnessed synergistic benefit amongst all CVH metrics. To achieve holistic management, future research should address the feasibility, adherence, and cost-effectiveness of simultaneous lifestyle modifications and drug therapy and their potential for enhanced health outcomes. Beyond, current clinical guidelines define target levels based on age, comorbidities, and disease progression (ie. the treatment systolic blood pressure goal for CKD patients without albuminuria is <140 mmHg whereas those with albuminuria is <130 mmHg based on the 2018 Korean Society of Hypertension's treatment guideline). In align, future metrics may enhance its prediction through more meticulous incorporation of patient demographics and disease history.

A major strength of our investigation was repeated assessments of CVH over a long horizon with high follow-up attendance and low attrition rate in a

large cohort. Because the KoGES Ansung-Ansan cohort was initially designed to provide detailed distributions of and levels on chronic diseases risks, the participants were thoroughly characterized for this study objectives.

However, several limitations warrant cautious interpretations. Due to the nature of the CVH scoring system, we were unable to pinpoint specific CVH metric(s) responsible for varied risk level. As previous study[44] reported age-varying effects of CVD risk factors in both independent and interactive manners, a larger study is needed to adequately assess differential contributions of each component. Regarding study design, CVD outcomes were self-reported instead of physician adjudication or cross-examination of medical records; therefore, recall bias may be possible. However, as high percentage of hospitalization and prolonged treatment is expected from hard cardiovascular events, we expect low misclassification rate. Residual confounding is also possible due to a lack of data on family history of CVD, genetic susceptibility, and more. Linkage to multigenerational health data or coronary artery disease polygenic risk score may help to provide tailored approaches to CVH prediction and management. Due to the nature of observational study, we were unable to calculate absolute risk reduction from ideal CVH maintenance. Pragmatic trials at general practice settings may encourage comprehensive and sustained CVH monitoring. Lastly, participants excluded in the analyses had worse glycemic and renal health albeit comparable age and sex distribution compared to the included individuals. Furthermore, when compared to the nationally representative sample of same age group residing in the same province, our study population had higher prevalence

of hypertension and hypercholesterolemia (Appendix Table 22). Therefore, our findings may not be entirely generalizable to all Korean population. Future nationwide study should elucidate potential geographic variations in CVH management status. Likewise, Korean-population specific metrics and their cutoffs should be developed and validated for feasible CVD management.

# V. Conclusion

Our findings suggest that longer maintenance of ideal CVH in midlife is associated with lowered CKD and CVD risks. Considering the rapidly aging population with growing economic and productivity burden associated with cardiometabolic diseases, our results underline the utmost need for primordial and primary prevention via active participation from both clinicians and patients throughout the life course. Nationwide public health programs should widen the opportunity window for early diagnosis across all age spectrum. In healthcare settings, practitioners should actively cooperate with patients to evaluate their circumstances for lifestyle modifications, to identify potential barriers (i.e., physical and social environment), to implement measurable goals, and to monitor their progress.

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# Appendix

## Appendix Methods. Statistical procedures of clinical cardiovascular health score trajectory analysis

To examine whether changes in clinical cardiovascular health score (0-8 point scale based on body mass index, blood pressure, fasting glucose, and total cholesterol categories) are associated with chronic kidney disease and cardiovascular risks, participants with 2 or greater follow-up attendance were included in latent class trajectory modeling using the SAS procedure *PROC TRAJ*.[1] Based on the previous literature,[2] we selected the optimal fit model based on 1) the Bayesian information criterion; 2) the average posterior predictive probability of group membership after 20 multiple imputations; and 3) modification of the number of clusters from 3 to 5 with various combinations of polynomial functions (linear, quadratic, and tertiary).

After confirming the satisfaction of proportional hazards assumption, we set the trajectory group membership as an independent variable in multivariate Cox hazards regression model. Model 1 adjusted for baseline age, sex, examination site, education level, cigarette smoking, alcohol drinking, and physical activity; we additionally adjusted for baseline estimated glomerular filtration rate and urine albumin-to-creatinine ratio for chronic kidney disease as an outcome. In model 2, we additionally adjusted for baseline cardiovascular health score. Model calibration was ensured based on the Hosmer-Lemeshow goodness-of-fit statistics.

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**Appendix Table 1. Baseline characteristics of study participants by sex**

| Characteristic | Male (n=3,843) | Female (n=4,177) |
|---|---|---|
| Age, year | 51.29±8.63 | 52.32±8.97 |
| Attained high school degree | 1,555 (40.46) | 1,381 (33.06) |
| Body mass index, kg/m$^2$ | 24.28±2.91 | 24.92±3.30 |
| Current smoker | 1,856 (48.30) | 158 (3.78) |
| Current drinker | 2,754 (71.66) | 1,123 (26.89) |
| MVPA 150+ min/week | 2,331 (60.66) | 2,421 (57.96) |
| Systolic blood pressure, mmHg | 122.28±17.08 | 121.08±19.85 |
| Diastolic blood pressure, mmHg | 82.29±11.21 | 79.11±12.01 |
| Hypertension | 1,374 (35.75) | 1,360 (32.56) |
| Total cholesterol, mg/dL | 199.26±36.15 | 199.18±36.26 |
| HDL cholesterol, mg/dL | 47.52±11.36 | 51.19±11.77 |
| Fasting blood glucose level, mg/dL | 94.78±24.53 | 90.02±19.56 |
| Diabetes mellitus | 212 (5.52) | 144 (3.45) |
| eGFR, ml/min/1.73m$^2$ | 90.95±14.51 | 95.46±15.77 |
| Chronic kidney disease | 70 (1.82) | 96 (2.30) |
| Cardiovascular disease | 124 (3.23) | 100 (2.39) |
| Coronary artery disease | 74 (1.93) | 54 (1.29) |
| Cerebrovascular disease | 50 (1.30) | 41 (0.98) |
| Heart failure | 9 (0.23) | 9 (0.22) |
| Cardiovascular health score category | | |
| Ideal (12-14) | 164 (4.27) | 973 (23.29) |
| Intermediate (8-11) | 1,870 (48.66) | 2,601 (62.27) |
| Poor (0-7) | 1,809 (47.07) | 603 (14.44) |
| Cardiovascular health score (%) | | |
| 0 points | 1 (0.03) | 1 (0.02) |
| 1 point | 15 (0.39) | 0 (0.0) |
| 2 points | 29 (0.75) | 2 (0.05) |
| 3 points | 93 (2.42) | 9 (0.22) |
| 4 points | 209 (5.44) | 30 (0.72) |
| 5 points | 335 (8.72) | 78 (1.87) |
| 6 points | 485 (12.62) | 184 (4.41) |
| 7 points | 642 (16.1) | 299 (7.16) |
| 8 points | 650 (16.91) | 475 (11.37) |
| 9 points | 579 (15.07) | 641 (15.35) |
| 10 points | 409 (10.64) | 760 (18.19) |
| 11 points | 232 (6.04) | 725 (17.36) |
| 12 points | 113 (2.94) | 544 (13.02) |
| 13 points | 35 (0.91) | 288 (6.89) |
| 14 points | 16 (0.42) | 141 (3.38) |

*Values are presented as mean±standard deviation or number (%).

Abbreviations: eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; MVPA, moderate-vigorous physical activity

**Appendix Table 2. Comparison of participants included versus excluded in the study**

| Characteristic | Included (n=8,020) | Excluded (n=818) | *p*-value |
|---|---|---|---|
| Male sex | 3,843 (47.92) | 438 (53.55) | 0.4250 |
| Age, year | 51.83±8.82 | 51.62±9.10 | 0.5152 |
| Attained high school degree | 3,669 (45.75) | 357 (43.64) | 0.2495 |
| Body mass index, kg/m$^2$ | 24.61±3.14 | 24.45±3.17 | 0.1645 |
| Current smoker | 2,014 (25.11) | 238 (29.10) | 0.0383 |
| Current drinker | 3,877 (48.34) | 374 (45.72) | 0.2961 |
| MVPA 150+ min/week | 4,752 (59.25) | 383 (46.82) | <0.0001 |
| Systolic blood pressure, mmHg | 121.65±18.58 | 122.55±20.25 | 0.1950 |
| Diastolic blood pressure, mmHg | 80.64±11.74 | 80.47±12.24 | 0.7041 |
| Hypertension | 2,734 (34.09) | 295 (36.06) | 0.5851 |
| Total cholesterol, mg/dL | 199.21±36.20 | 201.39±41.27 | 0.1055 |
| HDL cholesterol, mg/dL | 49.43±11.72 | 49.96±12.57 | 0.2227 |
| Fasting glucose level, mg/dL | 92.30±22.21 | 95.43±30.32 | 0.0002 |
| Diabetes mellitus | 356 (4.44) | 52 (6.36) | <0.0001 |
| eGFR, ml/min/1.73m$^2$ | 93.30±15.35 | 91.83±16.94 | 0.0096 |
| Chronic kidney disease | 166 (2.07) | 23 (2.81) | 0.1624 |
| Cardiovascular disease | 224 (2.79) | 25 (3.06) | 0.6648 |
| Coronary artery disease | 128 (1.60) | 14 (1.71) | 0.8035 |
| Cerebrovascular disease | 91 (1.14) | 11 (1.34) | 0.5929 |
| Heart failure | 18 (0.22) | 0 (0.0) | 0.1749 |
| CVH score category | | | 0.0017 |
| Ideal (12-14) | 1,137 (14.18) | 103 (12.59) | |
| Intermediate (8-11) | 4,471 (55.75) | 421 (51.47) | |
| Poor (0-7) | 2,412 (30.07) | 294 (35.94) | |

*Values are presented as mean±standard deviation or number (%).

Abbreviations: CVH, cardiovascular health; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; MVPA, moderate-vigorous physical activity

**Appendix Table 3. Distribution of the duration of each ideal cardiovascular health metric and total score**

| Metric | Mean | Minimum | Percentile | | | | Maximum |
|---|---|---|---|---|---|---|---|
| | | | 25th | 50th | 75th | 90th | |
| Without CKD at baseline (n=7,854) | | | | | | | |
| Ideal CVH score | 1.41 | 0.00 | 0.00 | 0.00 | 1.67 | 5.75 | 15.50 |
| Ideal smoking | 8.56 | 0.00 | 0.00 | 13.58 | 14.00 | 14.58 | 15.50 |
| Ideal physical activity | 4.91 | 0.00 | 1.75 | 3.75 | 7.92 | 12.17 | 15.50 |
| Ideal alcohol drinking | 6.64 | 0.00 | 0.00 | 5.75 | 13.75 | 14.25 | 15.50 |
| Ideal body mass index | 4.55 | 0.00 | 0.00 | 0.00 | 11.50 | 14.08 | 15.50 |
| Ideal blood pressure | 5.18 | 0.00 | 0.00 | 2.42 | 10.33 | 13.83 | 15.50 |
| Ideal fasting glucose | 10.55 | 0.00 | 7.83 | 13.50 | 14.00 | 14.58 | 15.50 |
| Ideal total cholesterol | 7.83 | 0.00 | 2.08 | 8.17 | 13.58 | 14.25 | 15.50 |
| Without CVD at baseline (n=7,796) | | | | | | | |
| Ideal CVH score | 1.42 | 0.00 | 0.00 | 0.00 | 1.67 | 5.75 | 15.50 |
| Ideal smoking | 8.59 | 0.00 | 0.00 | 13.58 | 14.00 | 14.58 | 15.50 |
| Ideal physical activity | 4.90 | 0.00 | 1.75 | 3.75 | 7.92 | 12.17 | 15.50 |
| Ideal alcohol drinking | 6.66 | 0.00 | 0.00 | 5.83 | 13.75 | 14.25 | 15.50 |
| Ideal body mass index | 4.56 | 0.00 | 0.00 | 0.00 | 11.50 | 14.08 | 15.50 |
| Ideal blood pressure | 5.18 | 0.00 | 0.00 | 2.42 | 10.33 | 13.83 | 15.50 |
| Ideal fasting glucose | 10.56 | 0.00 | 7.83 | 13.58 | 14.00 | 14.58 | 15.50 |
| Ideal total cholesterol | 7.82 | 0.00 | 2.08 | 8.17 | 13.58 | 14.17 | 15.50 |

*The unit is in years.

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; CVH, cardiovascular health

**Appendix Table 4. Correlation between baseline cardiovascular health score and ideal cardiovascular health duration**

| Variables | Baseline CVH score | Baseline smoking | Baseline physical activity | Baseline alcohol drinking | Baseline body mass index | Baseline blood pressure | Baseline fasting glucose | Baseline total cholesterol |
|---|---|---|---|---|---|---|---|---|
| Dur. ideal CVH | 0.61[c] | 0.36[c] | 0.05[c] | 0.36[c] | 0.37[c] | 0.34[c] | 0.18[c] | 0.22[c] |
| Dur. ideal smoking | 0.46[c] | 0.85[c] | -0.01 | 0.44[c] | -0.06[c] | 0.02 | 0.10[c] | 0.02[a] |
| Dur. ideal physical activity | 0.02 | -0.01 | 0.26[c] | -0.08[c] | -0.06[c] | 0.03[a] | -0.05[c] | -0.05[c] |
| Dur. ideal alcohol drinking | 0.50[c] | 0.51[c] | -0.02 | 0.82[c] | -0.02 | 0.02 | 0.09[c] | -0.01 |
| Dur. ideal body mass index | 0.37[c] | -0.05[c] | 0.01 | 0.01 | 0.83[c] | 0.16[c] | 0.10[c] | 0.14[c] |
| Dur. ideal blood pressure | 0.34[c] | 0.05[c] | -0.08[c] | 0.03[b] | 0.22[c] | 0.73[c] | 0.14[c] | 0.11[c] |
| Dur. ideal fasting glucose | 0.32[c] | 0.14[c] | -0.02 | 0.12[c] | 0.17[c] | 0.17[c] | 0.56[c] | 0.11[c] |
| Dur. ideal total cholesterol | 0.21[c] | -0.09[c] | 0.07[c] | -0.05[c] | 0.13[c] | 0.03[b] | 0.02 | 0.67[c] |

The correlation coefficients are obtained from Spearman correlation.

[a]*p*-value <0.05

[b]*p*-value <0.01

[c]*p*-value <0.001

Abbreviations: CVH, cardiovascular health; Dur., duration

**Appendix Table 5. Association of maintaining ideal cardiovascular health with risk of developing chronic kidney disease or cardiovascular disease on follow-up, excluding incidence during the first follow-up wave**

| Outcome | Ideal CVH Duration | No. of Events/No. at Risk (%) | HR (95% CI) | *P* trend |
|---|---|---|---|---|
| †Chronic kidney disease | <5 years | 1,255/7,000 (17.93) | 1.00 Reference | |
| | 5 to 10 years | 47/518 (9.07) | 0.67 (0.41-0.98) | 0.0071 |
| | ≥10 years | 21/336 (6.25) | 0.29 (0.12-0.71) | |
| ‡Cardiovascular disease | <5 years | 404/6,939 (5.82) | 1.00 Reference | |
| | 5 to 10 years | 20/523 (3.82) | 0.85 (0.54-1.35) | 0.0245 |
| | ≥10 years | 4/334 (1.20) | 0.26 (0.10-0.70) | |
| Coronary artery disease | <5 years | 229/7,031 (3.26) | 1.00 Reference | |
| | 5 to 10 years | 6/524 (1.15) | 0.44 (0.19-0.99) | 0.0182 |
| | ≥10 years | 2/337 (0.59) | 0.23 (0.06-0.92) | |
| Cerebrovascular disease | <5 years | 193/7,070 (2.73) | 1.00 Reference | |
| | 5 to 10 years | 14/524 (2.67) | 1.41 (0.81-2.45) | 0.2302 |
| | ≥10 years | 2/335 (0.60) | 0.31 (0.08-1.25) | |
| Heart failure | <5 years | 8/6,939 (0.12) | 1.00 Reference | |
| | 5 to 10 years | 1/523 (0.19) | 1.32 (0.16-11.04) | 0.8010 |
| | ≥10 years | 0/334 (0.0) | N/A | |

*All models adjusted for age, sex, education level, and examination site.

†Additionally adjusted for baseline estimated glomerular filtration rate and urine albumin-to-creatinine ratio

‡First cardiovascular disease event: coronary artery disease, cerebrovascular disease, or heart failure

Abbreviations: CI, confidence interval; CVH, cardiovascular health; HR, hazard ratio

**Appendix Table 6. Association of maintaining ideal cardiovascular health with risk of developing chronic kidney disease or cardiovascular disease on follow-up among participants who have attended at least 4 follow-up examinations**

| Outcome | Ideal CVH Duration | No. of Events/No. at Risk (%) | HR (95% CI) | *P* trend |
|---|---|---|---|---|
| †Chronic kidney disease | <5 years | 1,148/5,344 (21.48) | 1.00 Reference | |
| | 5 to 10 years | 45/488 (9.22) | 0.70 (0.31-0.98) | 0.0231 |
| | ≥10 years | 18/186 (9.68) | 0.41 (0.19-0.87) | |
| ‡Cardiovascular disease | <5 years | 390/5,308 (7.35) | 1.00 Reference | |
| | 5 to 10 years | 23/493 (4.67) | 0.80 (0.52-1.26) | 0.0284 |
| | ≥10 years | 4/186 (2.15) | 0.40 (0.15-0.87) | |
| Coronary artery disease | <5 years | 237/5,365 (4.42) | 1.00 Reference | |
| | 5 to 10 years | 7/494 (1.42) | 0.39 (0.18-0.84) | 0.0174 |
| | ≥10 years | 2/187 (1.07) | 0.33 (0.08-1.02) | |
| Cerebrovascular disease | <5 years | 170/5,395 (3.15) | 1.00 Reference | |
| | 5 to 10 years | 16/494 (3.24) | 1.43 (0.84-2.43) | 0.2540 |
| | ≥10 years | 2/186 (1.08) | 0.52 (0.13-2.12) | |
| Heart failure | <5 years | 8/5,987 (0.13) | 1.00 Reference | |
| | 5 to 10 years | 1/493 (0.20) | 1.30 (0.15-11.16) | 0.8138 |
| | ≥10 years | 0/186 (0.0) | N/A | |

*All models adjusted for age, sex, education level, and examination site.

†Additionally adjusted for baseline estimated glomerular filtration rate and urine albumin-to-creatinine ratio

‡First cardiovascular disease event: coronary artery disease, cerebrovascular disease, or heart failure

Abbreviations: CI, confidence interval; CVH, cardiovascular health; HR, hazard ratio

**Appendix Table 7. Association of maintaining ideal cardiovascular health with risk of developing chronic kidney disease or cardiovascular disease on follow-up among participants who have attended at least 5 follow-up examinations**

| Outcome | Ideal CVH Duration | No. of Events/No. at Risk (%) | HR (95% CI) | *P* trend |
|---|---|---|---|---|
| †Chronic kidney disease | <5 years | 1,057/4,880 (21.66) | 1.00 Reference | |
| | 5 to 10 years | 45/463 (9.72) | 0.59 (0.35-0.99) | 0.0326 |
| | ≥10 years | 14/168 (8.33) | 0.45 (0.16-0.98) | |
| ‡Cardiovascular disease | <5 years | 360/4,846 (7.43) | 1.00 Reference | |
| | 5 to 10 years | 21/469 (4.48) | 0.75 (0.48-1.07) | 0.0192 |
| | ≥10 years | 4/168 (2.38) | 0.44 (0.16-0.97) | |
| Coronary artery disease | <5 years | 219/4,846 (4.52) | 1.00 Reference | |
| | 5 to 10 years | 6/469 (1.28) | 0.35 (0.15-0.79) | 0.0164 |
| | ≥10 years | 2/168 (1.19) | 0.31 (0.08-1.05) | |
| Cerebrovascular disease | <5 years | 148/4/,846 (3.05) | 1.00 Reference | |
| | 5 to 10 years | 15/469 (3.20) | 1.40 (0.81-2.41) | 0.3384 |
| | ≥10 years | 2/168 (1.19) | 0.57 (0.14-2.13) | |
| Heart failure | <5 years | 7/4,846 (0.14) | 1.00 Reference | |
| | 5 to 10 years | 0/469 (0.0) | N/A | N/A |
| | ≥10 years | 0/168 (0.0) | N/A | |

*All models adjusted for age, sex, education level, and examination site.

†Additionally adjusted for baseline estimated glomerular filtration rate and urine albumin-to-creatinine ratio

‡First cardiovascular disease event: coronary artery disease, cerebrovascular disease, or heart failure

Abbreviations: CI, confidence interval; CVH, cardiovascular health; HR, hazard ratio

**Appendix Table 8. Association of maintaining ideal cardiovascular health with risk of developing chronic kidney disease or cardiovascular disease on follow-up among participants who have attended at least 6 follow-up examinations**

| Outcome | Ideal CVH Duration | No. of Events/No. at Risk (%) | HR (95% CI) | *P* trend |
|---|---|---|---|---|
| †Chronic kidney disease | <5 years | 920/4,279 (21.50) | 1.00 Reference | |
| | 5 to 10 years | 39/418 (9.33) | 0.52 (0.29-0.92) | 0.0343 |
| | ≥10 years | 13/145 (8.97) | 0.47 (0.18-1.07) | |
| ‡Cardiovascular disease | <5 years | 322/4,246 (7.58) | 1.00 Reference | |
| | 5 to 10 years | 16/422 (3.79) | 0.63 (0.38-0.95) | 0.0373 |
| | ≥10 years | 4/145 (2.76) | 0.50 (0.18-1.13) | |
| Coronary artery disease | <5 years | 196/4,246 (4.62) | 1.00 Reference | |
| | 5 to 10 years | 6/422 (1.42) | 0.39 (0.17-0.88) | 0.0370 |
| | ≥10 years | 2/145 (1.38) | 0.37 (0.10-1.15) | |
| Cerebrovascular disease | <5 years | 132/4,246 (3.11) | 1.00 Reference | |
| | 5 to 10 years | 10/422 (2.37) | 1.29 (0.54-2.02) | 0.2844 |
| | ≥10 years | 2/145 (1.38) | 0.66 (0.16-2.70) | |
| Heart failure | <5 years | 7/4,813 (0.15) | 1.00 Reference | |
| | 5 to 10 years | 0/422 (0.0) | N/A | N/A |
| | ≥10 years | 0/145 (0.0) | N/A | |

*All models adjusted for age, sex, education level, and examination site.

†Additionally adjusted for baseline estimated glomerular filtration rate and urine albumin-to-creatinine ratio

‡First cardiovascular disease event: coronary artery disease, cerebrovascular disease, or heart failure

Abbreviations: CI, confidence interval; CVH, cardiovascular health; HR, hazard ratio

**Appendix Table 9. Association of maintaining ideal cardiovascular health with risk of developing chronic kidney disease or cardiovascular disease on follow-up among participants who have attended all follow-up examinations**

| Outcome | Ideal CVH Duration | No. of Events/No. at Risk (%) | HR (95% CI) | *P* trend |
|---|---|---|---|---|
| †Chronic kidney disease | <5 years | 697/3,282 (21.24) | 1.00 Reference | |
| | 5 to 10 years | 27/321 (8.41) | 0.47 (0.24-0.92) | 0.0517 |
| | ≥10 years | 10/113 (8.85) | 0.52 (0.15-1.42) | |
| ‡Cardiovascular disease | <5 years | 244/3,247 (7.51) | 1.00 Reference | |
| | 5 to 10 years | 14/323 (4.33) | 0.74 (0.43-1.19) | 0.1199 |
| | ≥10 years | 4/113 (3.54) | 0.65 (0.24-1.56) | |
| Coronary artery disease | <5 years | 150/3,247 (4.62) | 1.00 Reference | |
| | 5 to 10 years | 5/323 (1.55) | 0.42 (0.17-0.94) | 0.0927 |
| | ≥10 years | 2/113 (1.77) | 0.52 (0.13-1.55) | |
| Cerebrovascular disease | <5 years | 99/3,247 (3.05) | 1.00 Reference | |
| | 5 to 10 years | 9/323 (2.79) | 1.29 (0.64-2.60) | 0.4096 |
| | ≥10 years | 2/113 (1.77) | 0.79 (0.22-3.26) | |
| Heart failure | <5 years | 4/3,247 (0.12) | 1.00 Reference | |
| | 5 to 10 years | 0/323 (0.0) | N/A | N/A |
| | ≥10 years | 0/113 (0.0) | N/A | |

*All models adjusted for age, sex, education level, and examination site.

†Additionally adjusted for baseline estimated glomerular filtration rate and urine albumin-to-creatinine ratio

‡First cardiovascular disease event: coronary artery disease, cerebrovascular disease, or heart failure

Abbreviations: CI, confidence interval; CVH, cardiovascular health; HR, hazard ratio

**Appendix Table 10. Association of maintaining ideal cardiovascular health with risk of developing chronic kidney disease or cardiovascular disease on follow-up among participants below the median follow-up time**

| Outcome | Ideal CVH Duration | No. of Events/No. at Risk (%) | HR (95% CI) | *P* trend |
|---|---|---|---|---|
| †Chronic kidney disease | <5 years | 1,329/3,428 (38.77) | 1.00 Reference | |
| | 5 to 10 years | 49/308 (15.91) | 0.53 (0.32-0.86) | 0.0132 |
| | ≥10 years | 23/125 (18.40) | 0.53 (0.24-1.19) | |
| ‡Cardiovascular disease | <5 years | 466/3,246 (14.36) | 1.00 Reference | |
| | 5 to 10 years | 23/332 (6.93) | 0.68 (0.44-1.04) | 0.0336 |
| | ≥10 years | 4/119 (3.36) | 0.37 (0.14-0.99) | |
| Coronary artery disease | <5 years | 276/3,167 (8.71) | 1.00 Reference | |
| | 5 to 10 years | 7/324 (2.16) | 0.45 (0.14-0.75) | 0.0180 |
| | ≥10 years | 3/122 (2.46) | 0.35 (0.06-1.15) | |
| Cerebrovascular disease | <5 years | 217/3,169 (6.85) | 1.00 Reference | |
| | 5 to 10 years | 16/329 (4.86) | 1.15 (0.69-1.94) | 0.4861 |
| | ≥10 years | 2/118 (1.69) | 0.47 (0.12-1.92) | |
| Heart failure | <5 years | 11/3,797 (0.29) | 1.00 Reference | |
| | 5 to 10 years | 1/386 (0.26) | 0.92 (0.11-7.52) | 0.9972 |
| | ≥10 years | 0/150 (0.0) | N/A | |

*All models adjusted for age, sex, education level, and examination site.

†Additionally adjusted for baseline estimated glomerular filtration rate and urine albumin-to-creatinine ratio

‡First cardiovascular disease event: coronary artery disease, cerebrovascular disease, or heart failure

Abbreviations: CI, confidence interval; CVH, cardiovascular health; HR, hazard ratio

**Appendix Table 11. Association of maintaining ideal cardiovascular health with risk of developing chronic kidney disease or cardiovascular disease on follow-up based on the stagnant model**

| Outcome | Ideal CVH Duration | No. of Events/No. at Risk (%) | HR (95% CI) | *P* trend |
|---|---|---|---|---|
| †Chronic kidney disease | <5 years | 1,298/6,819 (19.04) | 1.00 Reference | |
| | 5 to 10 years | 70/651 (10.75) | 0.68 (0.42-0.87) | 0.0027 |
| | ≥10 years | 33/384 (4.82) | 0.24 (0.07-0.69) | |
| ‡Cardiovascular disease | <5 years | 460/6,830 (6.73) | 1.00 Reference | |
| | 5 to 10 years | 28/595 (4.71) | 0.85 (0.57-1.22) | 0.0108 |
| | ≥10 years | 5/371 (1.35) | 0.26 (0.09-0.58) | |
| Coronary artery disease | <5 years | 260/6,830 (3.82) | 1.00 Reference | |
| | 5 to 10 years | 11/595 (1.85) | 0.48 (0.23-0.88) | 0.0402 |
| | ≥10 years | 3/371 (0.81) | 0.23 (0.08-0.73) | |
| Cerebrovascular disease | <5 years | 210/6,830 (3.07) | 1.00 Reference | |
| | 5 to 10 years | 17/595 (2.86) | 0.96 (0.38-1.81) | 0.0387 |
| | ≥10 years | 2/371 (0.54) | 0.24 (0.01-1.03) | |
| Heart failure | <5 years | 9/6,830 (0.13) | 1.00 Reference | |
| | 5 to 10 years | 1/595 (0.17) | 1.04 (0.07-9.63) | 0.9657 |
| | ≥10 years | 0/371 (0.0) | N/A | |

*All models adjusted for age, sex, education level, and examination site.

†Additionally adjusted for baseline estimated glomerular filtration rate and urine albumin-to-creatinine ratio

‡First cardiovascular disease event: coronary artery disease, cerebrovascular disease, or heart failure

Abbreviations: CI, confidence interval; CVH, cardiovascular health; HR, hazard ratio

**Appendix Table 12. Association of maintaining ideal cardiovascular health with risk of developing chronic kidney disease or cardiovascular disease on follow-up, excluding participants with very low clinical cardiovascular health metrics level**

| Outcome | Ideal CVH Duration | No. of Events/No. at Risk (%) | HR (95% CI) | *P* trend |
|---|---|---|---|---|
| †Chronic kidney disease | <5 years | 1,246/6,565 (18.98) | 1.00 Reference | |
| | 5 to 10 years | 42/476 (8.82) | 0.61 (0.34-0.96) | 0.0068 |
| | ≥10 years | 20/296 (6.76) | 0.36 (0.16-0.80) | |
| ‡Cardiovascular disease | <5 years | 437/6,503 (6.72) | 1.00 Reference | |
| | 5 to 10 years | 20/480 (4.17) | 0.81 (0.51-1.24) | 0.0106 |
| | ≥10 years | 4/294 (1.36) | 0.25 (0.09-0.64) | |
| Coronary artery disease | <5 years | 253/6,503 (3.89) | 1.00 Reference | |
| | 5 to 10 years | 5/480 (1.04) | 0.32 (0.13-0.78) | 0.0042 |
| | ≥10 years | 2/294 (0.68) | 0.21 (0.05-0.84) | |
| Cerebrovascular disease | <5 years | 191/6,503 (2.94) | 1.00 Reference | |
| | 5 to 10 years | 15/480 (3.13) | 1.51 (0.88-2.59) | 0.0812 |
| | ≥10 years | 2/294 (0.68) | 0.32 (0.08-1.30) | |
| Heart failure | <5 years | 8/6,503 (0.12) | 1.00 Reference | |
| | 5 to 10 years | 0/480 (0.0) | N/A | N/A |
| | ≥10 years | 0/294 (0.0) | N/A | |

*All models adjusted for age, sex, education level, and examination site.

†Additionally adjusted for baseline estimated glomerular filtration rate and urine albumin-to-creatinine ratio

‡First cardiovascular disease event: coronary artery disease, cerebrovascular disease, or heart failure

§Very low clinical CVH metrics include body mass index <18.5 kg/m$^2$, low-density lipoprotein cholesterol <25 mg/dL, diastolic blood pressure <60 mm-Hg, or fasting glucose <70 mg/dL.

Abbreviations: CI, confidence interval; CVH, cardiovascular health; HR, hazard ratio

**Appendix Table 13. Association of maintaining ideal cardiovascular health with risk of developing chronic kidney disease or cardiovascular disease on follow-up, accounting for competing risks**

| Cause of Competing Risk | Outcome | Ideal CVH Duration | No. of Events/No. at Risk (%) | HR (95% CI) | *P* trend |
|---|---|---|---|---|---|
| CVD | †Chronic kidney disease | <5 years | 1,329/7,000 (18.99) | 1.00 Reference | 0.0055 |
| | | 5 to 10 years | 49/518 (9.46) | 0.62 (0.38-0.93) | |
| | | ≥10 years | 23/336 (6.85) | 0.32 (0.14-0.72) | |
| CKD | ‡Cardiovascular disease | <5 years | 466/6,939 (6.72) | 1.00 Reference | 0.0094 |
| | | 5 to 10 years | 23/523 (4.40) | 0.87 (0.57-1.24) | |
| | | ≥10 years | 4/334 (1.20) | 0.24 (0.09-0.64) | |
| Cancer | †Chronic kidney disease | <5 years | 1,329/7,000 (18.99) | 1.00 Reference | 0.0043 |
| | | 5 to 10 years | 49/518 (9.46) | 0.60 (0.35-0.88) | |
| | | ≥10 years | 23/336 (6.85) | 0.30 (0.17-0.75) | |
| | ‡Cardiovascular disease | <5 years | 466/6,939 (6.72) | 1.00 Reference | 0.0083 |
| | | 5 to 10 years | 23/523 (4.40) | 0.80 (0.53-1.22) | |
| | | ≥10 years | 4/334 (1.20) | 0.21 (0.08-0.59) | |

*All models adjusted for age, sex, education level, and examination site.

†Additionally adjusted for baseline estimated glomerular filtration rate and urine albumin-to-creatinine ratio

‡First cardiovascular disease event: coronary artery disease, cerebrovascular disease, or heart failure

Abbreviations: CI, confidence interval; CVH, cardiovascular health; HR, hazard ratio

**Appendix Table 14. Association of maintaining ideal cardiovascular health with risk of estimated glomerular filtration rate decline by 30% or greater on follow-up**

| Outcome | Ideal CVH Duration | No. of Events/No. at Risk (%) | HR (95% CI) | *P* trend |
|---|---|---|---|---|
| eGFR decline | <5 years | 2,564/7,000 (36.63) | 1.00 Reference | 0.0478 |
| | ≥5 years | 365/854 (42.74) | 0.85 (0.72-0.98) | |
| | <10 years | 2,796/7,504 (37.26) | 1.00 Reference | 0.0049 |
| | ≥10 years | 133/350 (38.00) | 0.66 (0.50-0.88) | |
| | <5 years | 2,564/7,000 (36.63) | 1.00 Reference | |
| | 5 to 10 years | 239/518 (46.14) | 0.87 (0.76-1.05) | 0.0170 |
| | ≥10 years | 126/336 (37.50) | 0.66 (0.49-0.88) | |

*The models adjusted for age, sex, education level, examination site, and baseline eGFR and UACR.

Abbreviations: CI, confidence interval; CVH, cardiovascular health; HR, hazard ratio; UACR, urine albumin-to-creatinine-ratio

**Appendix Table 15. Association of maintaining ideal or intermediate cardiovascular health with risk of developing chronic kidney disease or cardiovascular disease on follow-up**

| Outcome | Ideal CVH Duration | No. of Events/No. at Risk (%) | HR (95% CI) | *P* trend |
|---|---|---|---|---|
| †Chronic kidney disease | <5 years | 413/2,285 (18.07) | 1.00 Reference | |
| | 5 to 10 years | 319/1,348 (23.66) | 1.16 (0.91-1.48) | 0.0001 |
| | ≥10 years | 669/4,221 (15.85) | 0.73 (0.58-0.91) | |
| ‡Cardiovascular disease | <5 years | 181/2,265 (7.99) | 1.00 Reference | |
| | 5 to 10 years | 114/1,344 (8.48) | 1.06 (0.83-1.34) | <0.0001 |
| | ≥10 years | 198/4,187 (4.73) | 0.61 (0.49-0.75) | |
| Coronary artery disease | <5 years | 68/2,323 (2.93) | 1.00 Reference | |
| | 5 to 10 years | 47/1,369 (3.43) | 0.89 (0.78-1.07) | 0.0082 |
| | ≥10 years | 104/4,265 (2.44) | 0.74 (0.61-0.97) | |
| Cerebrovascular disease | <5 years | 99/2,321 (4.27) | 1.00 Reference | |
| | 5 to 10 years | 48/1,363 (3.52) | 0.83 (0.59-1.18) | 0.0702 |
| | ≥10 years | 88/4,245 (2.07) | 0.53 (0.39-0.72) | |
| Heart failure | <5 years | 6/2,340 (0.26) | 1.00 Reference | |
| | 5 to 10 years | 4/1,378 (0.29) | 0.82 (0.22-3.01) | 0.0264 |
| | ≥10 years | 2/4,248 (0.05) | 0.11 (0.02-0.58) | |

*All models adjusted for age, sex, education level, and examination site.

†Additionally adjusted for baseline estimated glomerular filtration rate and urine albumin-to-creatinine ratio

‡First cardiovascular disease event: coronary artery disease, cerebrovascular disease, or heart failure

Abbreviations: CI, confidence interval; CVH, cardiovascular health; HR, hazard ratio

**Appendix Table 16. Association of cardiovascular health pattern with risk of developing chronic kidney disease or cardiovascular disease on follow-up**

| Changes in CVH Category | Outcome | No. of Events/No. at Risk (%) | HR (95% CI) |
|---|---|---|---|
| Nearly all suboptimal | [#]Chronic kidney disease | 730/3,772 (19.35) | 1.00 Reference |
| Optimal then early decline to suboptimal | | 348/2,000 (17.40) | 0.89 (0.73-1.09) |
| Gradual decline to suboptimal | | 320/2006 (15.95) | 0.69 (0.54-0.81) |
| Consistently optimal | | 3/76 (3.95) | 0.43 (0.12-0.80) |
| Nearly all suboptimal | [**]Cardiovascular disease | 284/3,762 (7.55) | 1.00 Reference |
| Optimal then early decline to suboptimal | | 124/1,977 (6.27) | 0.84 (0.71-1.03) |
| Gradual decline to suboptimal | | 83/1,989 (4.17) | 0.65 (0.51-0.79) |
| Consistently optimal | | 2/68 (2.94) | 0.38 (0.07-0.85) |

[*]Optimal CVH category refers to ideal CVH category.

[+]Suboptimal CVH category refers to intermediate or poor CVH category.

[‡]The "Optimal then early decline to suboptimal" group includes participants whose optimal CVH category changes to suboptimal within the first follow-up visit (median 2.83 years from the baseline).

[§]The "Gradual decline to suboptimal" group includes participants whose optimal CVH category changes to suboptimal after the third follow-up visit (median 6.84 years from the baseline).

[¶]All models adjusted for age, sex, education level, and examination site.

[#]Additionally adjusted for baseline estimated glomerular filtration rate and urine albumin-to-creatinine ratio

[**]First cardiovascular disease event: coronary artery disease, cerebrovascular disease, or heart failure

Abbreviations: CI, confidence interval; CVH, cardiovascular health; HR, hazard ratio

**Appendix Table 17. Association of maintaining ideal clinical cardiovascular health with risk of developing chronic kidney disease or cardiovascular disease on follow-up**

| Outcome | Ideal Clinical CVH Duration | No. of Events/No. at Risk (%) | HR (95% CI) | *P* trend |
|---|---|---|---|---|
| | <5 years | 1,177/5,685 (20.70) | 1.00 Reference | |
| ‡Chronic kidney disease | 5 to 10 years | 112/856 (13.08) | 0.72 (0.61-0.85) | <0.0001 |
| | ≥10 years | 112/1,313 (8.53) | 0.43 (0.34-0.59) | |
| | <5 years | 407/5,641 (7.22) | 1.00 Reference | |
| §Cardiovascular disease | 5 to 10 years | 42/852 (4.93) | 0.71 (0.55-0.97) | <0.0001 |
| | ≥10 years | 44/1,303 (3.38) | 0.41 (0.29-0.66) | |
| | <5 years | 229/5,641 (4.06) | 1.00 Reference | |
| Coronary artery disease | 5 to 10 years | 24/852 (2.82) | 0.65 (0.40-0.88) | 0.0010 |
| | ≥10 years | 22/1,303 (1.69) | 0.42 (0.33-0.69) | |
| | <5 years | 184/5,641 (3.26) | 1.00 Reference | |
| Cerebrovascular disease | 5 to 10 years | 20/852 (2.35) | 0.74 (0.47-1.18) | 0.0485 |
| | ≥10 years | 24/1,303 (1.84) | 0.54 (0.39-0.88) | |
| | <5 years | 8/5,641 (0.14) | 1.00 Reference | |
| Heart failure | 5 to 10 years | 1/852 (0.12) | 0.88 (0.11-6.07) | 0.8617 |
| | ≥10 years | 1/1,303 (0.08) | 0.56 (0.07-4.35) | |

*Clinical CVH metrics include body mass index, blood pressure, fasting glucose, and total cholesterol.

†All models adjusted for age, sex, education level, and examination site.

‡Additionally adjusted for baseline estimated glomerular filtration rate and urine albumin-to-creatinine ratio

§First cardiovascular disease event: coronary artery disease, cerebrovascular disease, or heart failure

Abbreviations: CI, confidence interval; CVH, cardiovascular health; HR, hazard ratio

**Appendix Table 18. Association of maintaining ideal lifestyle cardiovascular health with risk of developing chronic kidney disease or cardiovascular disease on follow-up**

| Outcome | Ideal Lifestyle CVH Duration | No. of Events/No. at Risk (%) | HR (95% CI) | *P* trend |
|---|---|---|---|---|
| | <5 years | 1,186/6,343 (18.70) | 1.00 Reference | |
| ‡Chronic kidney disease | 5 to 10 years | 155/965 (16.06) | 0.83 (0.70-0.98) | 0.0001 |
| | ≥10 years | 60/546 (10.99) | 0.56 (0.32-0.81) | |
| | <5 years | 416/6,290 (6.61) | 1.00 Reference | |
| §Cardiovascular disease | 5 to 10 years | 56/970 (5.77) | 0.98 (0.84-1.28) | 0.0468 |
| | ≥10 years | 21/536 (3.92) | 0.67 (0.43-0.91) | |
| | <5 years | 239/6,290 (3.80) | 1.00 Reference | |
| Coronary artery disease | 5 to 10 years | 30/970 (3.19) | 0.78 (0.53-1.01) | 0.0172 |
| | ≥10 years | 6/536 (1.12) | 0.45 (0.22-0.92) | |
| | <5 years | 191/6,290 (3.04) | 1.00 Reference | |
| Cerebrovascular disease | 5 to 10 years | 24/970 (2.47) | 1.02 (0.64-1.50) | 0.1182 |
| | ≥10 years | 13/536 (2.43) | 0.85 (0.54-1.70) | |
| | <5 years | 9/6,290 (0.14) | 1.00 Reference | |
| Heart failure | 5 to 10 years | 1/970 (0.10) | 0.55 (0.07-4.44) | 0.8515 |
| | ≥10 years | 0/536 (0.0) | N/A | |

*Lifestyle CVH metrics include cigarette smoking, physical activity, and alcohol drinking.

+All models adjusted for age, sex, education level, and examination site.

‡Additionally adjusted for baseline estimated glomerular filtration rate and urine albumin-to-creatinine ratio

§First cardiovascular disease event: coronary artery disease, cerebrovascular disease, or heart failure

Abbreviations: CI, confidence interval; CVH, cardiovascular health; HR, hazard ratio

**Appendix Table 19. Association between clinical cardiovascular health score trajectory and risk of chronic kidney disease on follow-up**

| Clinical CVH score trajectory group | No. of Events/No. at Risk (%) | Model 1 | | Model 2 | |
|---|---|---|---|---|---|
| | | HR (95% CI) | *p*-value | HR (95% CI) | *p*-value |
| Low-stagnant | 300/979 (30.64) | Reference | | Reference | |
| Intermediate-early decline | 422/2,000 (21.10) | 0.75 (0.64-0.84) | <0.0001 | 0.80 (0.59-0.97) | 0.0001 |
| Intermediate-stagnant | 370/2,086 (17.74) | 0.69 (0.57-0.79) | <0.0001 | 0.72 (0.55-0.85) | 0.0004 |
| High-stagnant | 216/1,486 (14.54) | 0.62 (0.51-0.77) | <0.0001 | 0.66 (0.32-0.80) | <0.0001 |
| Optimal-late decline | 50/593 (8.43) | 0.41 (0.17-0.72) | <0.0001 | 0.45 (0.09-0.68) | <0.0001 |

*Model 1 is adjusted for age, sex, education level, examination site, and baseline smoking, physical activity, alcohol drinking, estimated glomerular filtration rate, and urine albumin-to-creatinine ratio.

†Model 2 is additionally adjusted for baseline CVH score.

Abbreviations: CI, confidence interval; CVH, cardiovascular health; HR, hazard ratio;

**Appendix Table 20. Association between clinical cardiovascular health score trajectory and risk of cardiovascular disease on follow-up**

| Clinical CVH score trajectory group | No. of Events/No. at Risk (%) | Model 1 | | Model 2 | |
|---|---|---|---|---|---|
| | | HR (95% CI) | *p*-value | HR (95% CI) | *p*-value |
| Low-stagnant | 174/979 (17.77) | Reference | | Reference | |
| Intermediate-early decline | 187/2,000 (9.35) | 0.72 (0.55-0.92) | 0.0002 | 0.77 (0.54-0.97) | 0.0008 |
| Intermediate-stagnant | 103/2,086 (4.94) | 0.65 (0.29-0.87) | <0.0001 | 0.70 (0.25-0.93) | 0.0001 |
| High-stagnant | 40/1,486 (2.69) | 0.51 (0.11-0.89) | <0.0001 | 0.58 (0.08-0.89) | 0.0001 |
| Optimal-late decline | 7/593 (1.18) | 0.29 (0.01-0.77) | <0.0001 | 0.37 (0.04-0.76) | <0.0001 |

*Model 1 is adjusted for age, sex, education level, examination site, and baseline smoking, physical activity, and alcohol drinking.

†Model 2 is additionally adjusted for baseline CVH score.

‡First cardiovascular disease event: coronary artery disease, cerebrovascular disease, or heart failure

Abbreviations: CI, confidence interval; CVH, cardiovascular health; HR, hazard ratio

**Appendix Table 21. Association of maintaining ideal cardiovascular health with risk of developing chronic kidney disease or cardiovascular disease on follow-up per 3-year increment**

| Outcome | Ideal CVH Duration | No. of Events/No. at Risk (%) | HR (95% CI) | *P* trend |
|---|---|---|---|---|
| †Chronic kidney disease | 0 years | 1,118/5,824 (19.20) | 1.00 Reference | 0.0039 |
| | <3 years | 150/795 (18.87) | 1.04 (0.81-1.16) | |
| | 3-6 years | 73/529 (13.80) | 0.70 (0.47-0.97) | |
| | ≥6 years | 60/706 (8.50) | 0.42 (0.25-0.68) | |
| ‡Cardiovascular disease | 0 years | 430/5,768 (7.45) | 1.00 Reference | <0.0001 |
| | <3 years | 31/793 (3.91) | 0.72 (0.56-0.88) | |
| | 3-6 years | 16/528 (3.03) | 0.46 (0.29-0.73) | |
| | ≥6 years | 16/707 (2.26) | 0.33 (0.19-0.59) | |
| Coronary artery disease | 0 years | 242/5,768 (4.20) | 1.00 Reference | <0.0001 |
| | <3 years | 21/793 (2.65) | 0.64 (0.41-0.96) | |
| | 3-6 years | 6/528 (1.14) | 0.28 (0.13-0.64) | |
| | ≥6 years | 6/707 (0.85) | 0.24 (0.10-0.53) | |
| Cerebrovascular disease | 0 years | 197/5,768 (3.42) | 1.00 Reference | 0.0120 |
| | <3 years | 14/793 (1.77) | 0.80 (0.46-1.40) | |
| | 3-6 years | 8/528 (1.52) | 0.45 (0.25-0.89) | |
| | ≥6 years | 9/707 (1.27) | 0.40 (0.17-0.84) | |
| Heart failure | 0 years | 9/5,768 (0.16) | 1.00 Reference | N/A |
| | <3 years | 0/793 (0.0) | N/A | |
| | 3-6 years | 1/528 (0.19) | 0.91 (0.11-6.44) | |
| | ≥6 years | 0/707 (0.0) | N/A | |

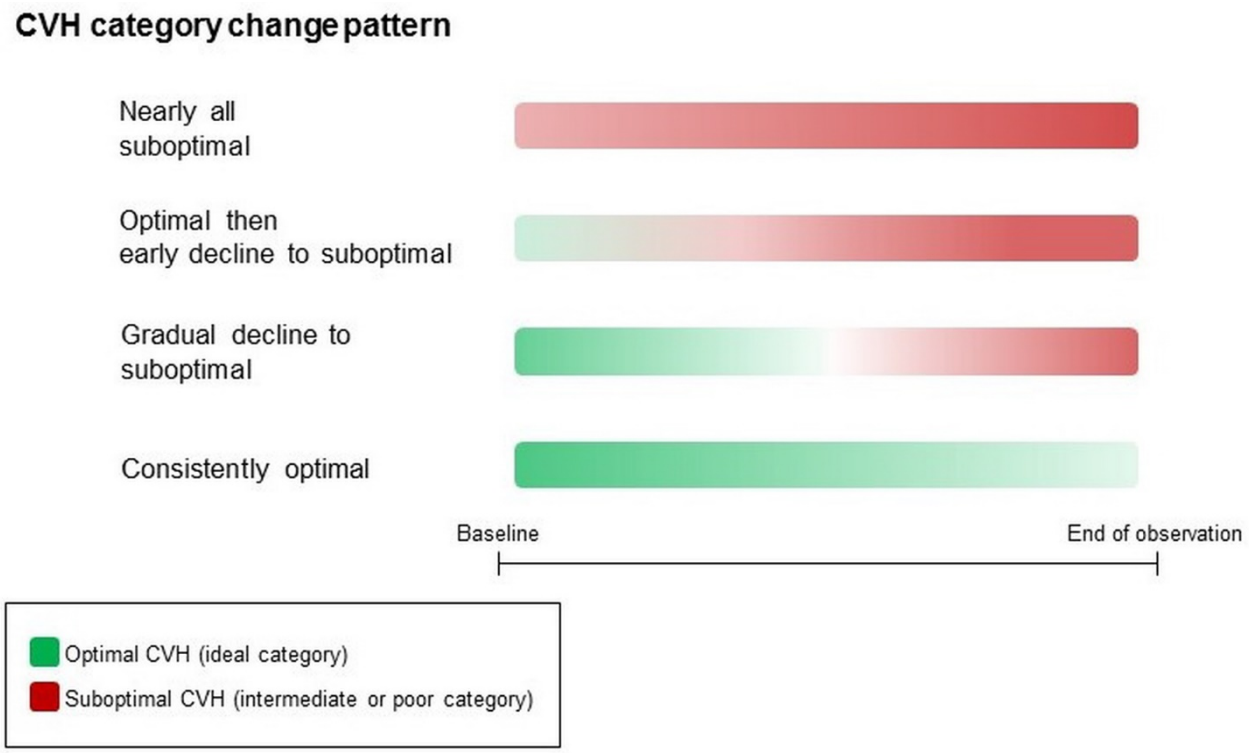
*All models adjusted for age, sex, education level, and examination site.
†Additionally adjusted for baseline estimated glomerular filtration rate and urine albumin-to-creatinine ratio
‡First cardiovascular disease event: coronary artery disease, cerebrovascular disease, or heart failure
Abbreviations: CI, confidence interval; CVH, cardiovascular health; HR, hazard ratio

**Appendix Table 22.** Comparison of baseline characteristics of Korean adults 40-69 years between the KoGES Ansung-Ansan cohort and nationwide sample

| Characteristic | Dataset | | *p*-value |
|---|---|---|---|
| | KoGES Ansung-Ansan (n=8,020) | KNHANES (n=286) | |
| Age | 51.83±8.82 | 51.16 (49.62-52.71) | 0.8310 |
| Sex | | | 0.0981 |
| Male | 47.92 | 50.82 (45.22-56.43) | |
| Female | 52.08 | 49.18 (43.57-54.78) | |
| Education level | | | 0.0584 |
| Below high school | 54.05 | 46.48 (33.67-59.29) | |
| High school | 31.81 | 34.29 (24.52-44.05) | |
| College/university or above | 14.14 | 19.23 (11.05-27.42) | |
| Body mass index, kg/m$^2$ | 24.61±3.14 | 24.20 (23.57-24.83) | |
| Total cholesterol, mg/dL | 199.21±36.20 | 194.80 (190.29-199.32) | 0.2341 |
| Triglyceride, mg/dL | 152.11±108.52 | 147.26 (138.91-155.62) | 0.1941 |
| HDL-cholesterol, mg/dL | 49.43±11.72 | 47.83 (46.16-49.51) | 0.0864 |
| Alcohol intake (drinks/wk) | | | 0.0671 |
| None | 48.34 | 44.57 (39.44-49.70) | |
| <3 per week | 6.17 | 5.14 (1.63-8.64) | |
| ≥3 per week | 45.49 | 50.29 (44.22-56.36) | |
| Smoking Status | | | 0.1071 |
| Never | 58.88 | 56.39 (50.69-62.10) | |
| Former | 16.01 | 19.18 (14.60-23.77) | |
| Current | 25.11 | 24.42 (18.15-30.70) | |
| Physical Activity | | | 0.0001 |
| 75+ min of vigorous or 150+ min of moderate activity | 59.25 | 31.79 (24.79-38.79) | |
| More than 0 min but less than the recommendation | 8.93 | 13.04 (9.02-17.06) | |
| 0 minutes | 31.82 | 55.17 (47.73-62.61) | |
| Body mass index | | | 0.0228 |
| Ideal | 43.07 | 38.43 (30.32-46.54) | |
| Intermediate | 26.31 | 22.05 (17.28-26.83) | |
| Poor | 30.62 | 39.52 (31.85-47.18) | |
| Total cholesterol, mg/dL | | | 0.0471 |
| <200 (Untreated) | 52.78 | 62.37 (54.95-69.80) | |
| 200-239 or treated to goal | 33.64 | 30.62 (23.86-37.38) | |
| ≥240 | 13.58 | 7.00 (3.17-10.83) | |

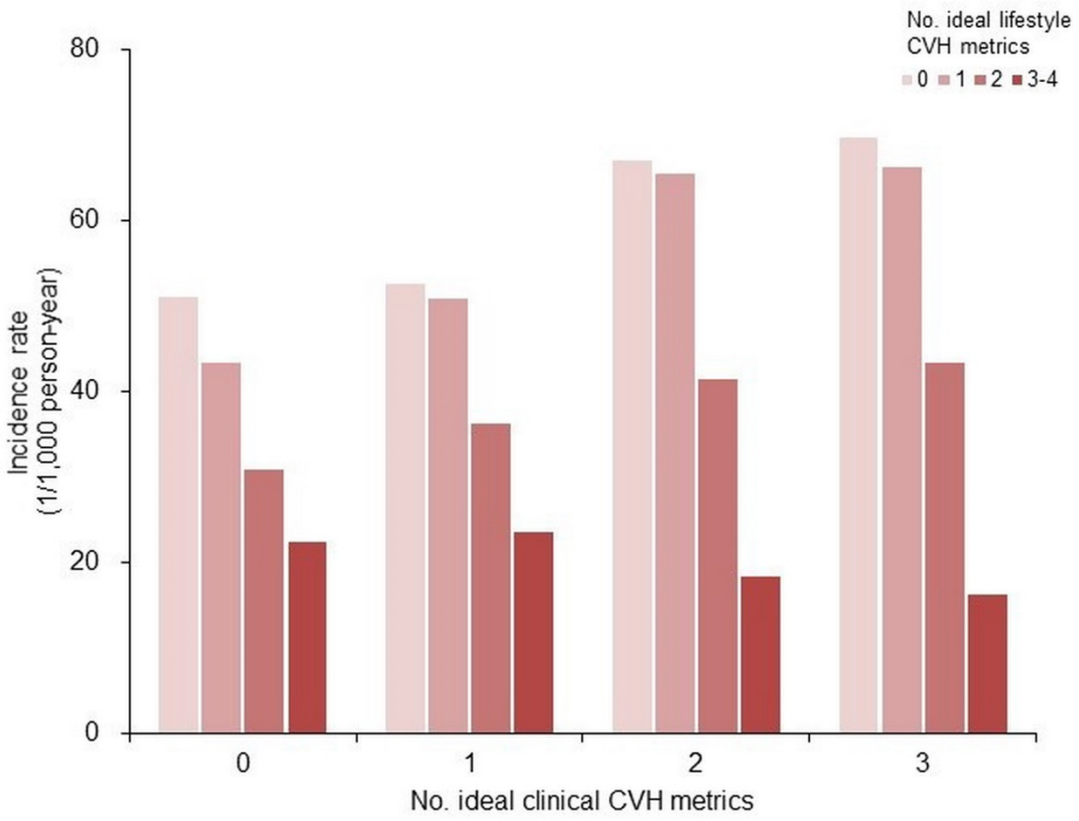
| | | | |
|---|---|---|---|
| Blood pressure, mmHg | | | <0.0001 |
| <120/80 (Untreated) | 35.02 | 50.38 (41.78-58.97) | |
| SBP 120-139 or DBP <90 or treated to goal | 43.88 | 36.51 (29.44-43.57) | |
| SBP ≥140 or DBP ≥90 | 21.10 | 13.11 (8.05-18.18) | |
| Fasting glucose, mg/dL | | | 0.0614 |
| <100 (Untreated) | 84.14 | 76.10 (66.98-85.22) | |
| 100-125 or treated to goal | 11.53 | 17.64 (11.44-23.84) | |
| ≥126 | 4.33 | 6.26 (1.39-11.12) | |

*The nationwide sample is derived from the KNHANES 2001, 2005, and 2007.
†For KoGES Ansung-Ansan data, values are presented as mean±standard deviation or percentage.
‡Due to complex, multi-stage probability sampling design of the KNHANES, the values are presented as weighted value (confidence intervals).
Abbreviations: DBP, diastolic blood pressure; HDL, high-density lipoprotein; KNHANES, The-Korea National Health and Nutrition Examination Survey; KoGES, The Korean Genome and Epidemiology Study; SBP, systolic blood pressure

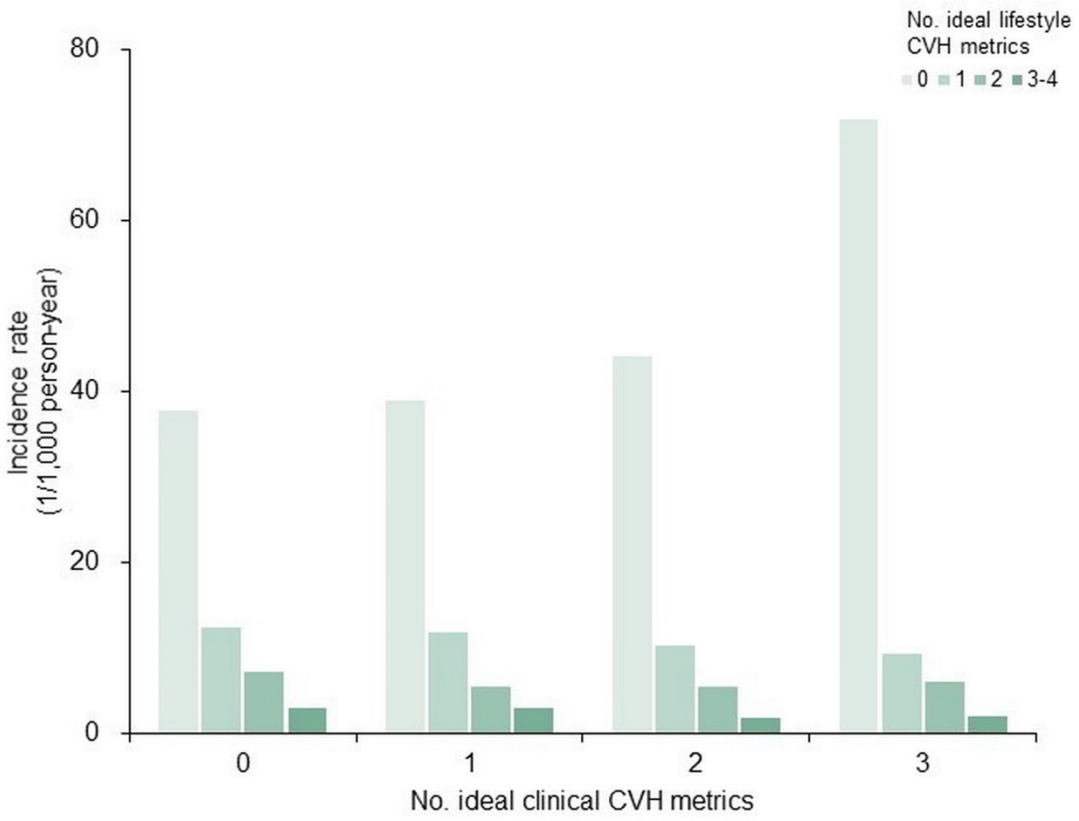



**Appendix Figure 1. Conceptual diagram of identified patterns of cardiovascular health (CVH) category change**

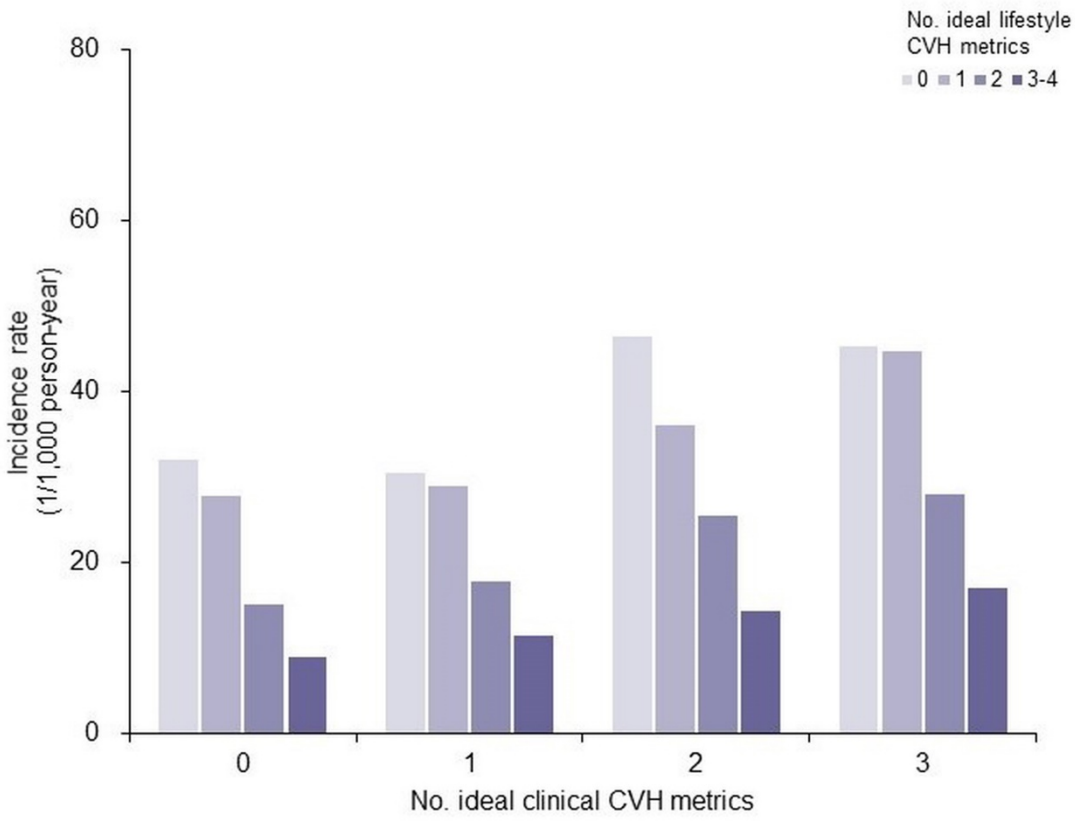
The “Optimal then early decline to suboptimal” group includes participants whose optimal CVH category changes to suboptimal within the first follow-up visit (median 2.83 years from the baseline).
The “Gradual decline to suboptimal” group includes participants whose optimal CVH category changes to suboptimal after the third follow-up visit (median 6.84 years from the baseline).




**Appendix Figure 2. Age- and sex-adjusted hypertension incidence by baseline number of ideal cardiovascular health (CVH) metrics**

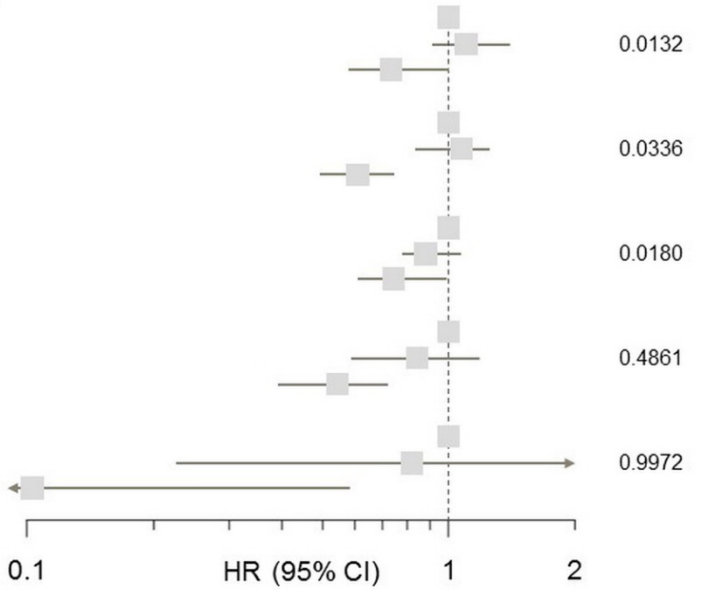



**Appendix Figure 3. Age- and sex-adjusted diabetes mellitus incidence by baseline number of ideal cardiovascular health (CVH) metrics**

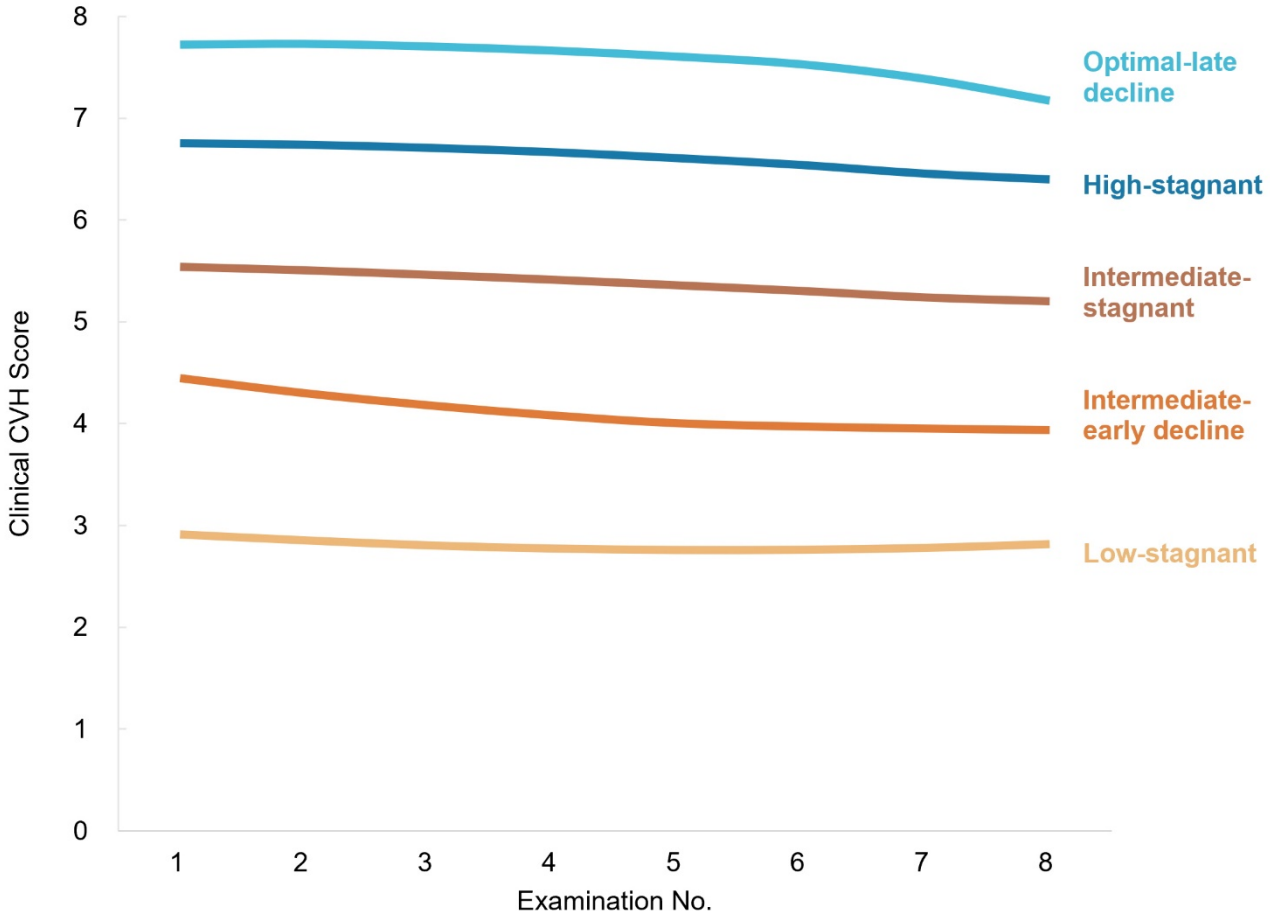



**Appendix Figure 4. Age- and sex-adjusted hypercholesterolemia incidence by baseline number of ideal cardiovascular health (CVH) metrics**

| Outcome | Ideal CVH Duration | No. of Events/ No. at Risk (%) | HR (95% CI) | *P* Trend |
|---|---|---|---|---|
| Chronic kidney disease | <5 years | 413/2,285 (18.07) | 1.00 Reference | 0.0132 |
| | 5 to 10 years | 319/1,348 (23.66) | 1.16 (0.91-1.48) | |
| | ≥10 years | 669/4,221 (15.85) | 0.73 (0.58-0.91) | |
| Cardiovascular disease | <5 years | 181/2,265 (7.99) | 1.00 Reference | 0.0336 |
| | 5 to 10 years | 114/1,344 (8.48) | 1.06 (0.83-1.34) | |
| | ≥10 years | 198/4,187 (4.73) | 0.61 (0.49-0.75) | |
| Coronary artery disease | <5 years | 68/2,323 (2.93) | 1.00 Reference | 0.0180 |
| | 5 to 10 years | 47/1,369 (3.43) | 0.89 (0.78-1.07) | |
| | ≥10 years | 104/4,265 (2.44) | 0.74 (0.61-0.97) | |
| Cerebrovascular disease | <5 years | 99/2,321 (4.27) | 1.00 Reference | 0.4861 |
| | 5 to 10 years | 48/1,363 (3.52) | 0.83 (0.59-1.18) | |
| | ≥10 years | 88/4,245 (2.07) | 0.53 (0.39-0.72) | |
| Heart failure | <5 years | 6/2,340 (0.26) | 1.00 Reference | 0.9972 |
| | 5 to 10 years | 4/1,378 (0.29) | 0.82 (0.22-3.01) | |
| | ≥10 years | 2/4,248 (0.05) | 0.11 (0.02-0.58) | |




**Appendix Figure 5. Forest plot of the association of ideal or intermediate cardiovascular health (CVH) duration with risk of chronic kidney disease and cardiovascular disease on follow-up**




**Appendix Figure 6. Clinical cardiovascular health (CVH) score trajectories across follow-up**

## Abstract (Korean)

# 이상적 심혈관건강지표 지속기간이 만성신장질환 및 심혈관질환 위험에 미치는 영향

연세대학교 일반대학원 보건학과

조소미

**서론**

최근 포괄적인 심혈관건강지표를 이용하여 심뇌혈관질환의 일·이차 예방 전략을 개발하는 시도가 증가하고 있다. 그러나 심혈관질환 위험도는 연령, 성별, 인종, 질병 과거력 등에 따라 다를 뿐 아니라 시간에 따른 위험요인의 변화 양상 및 누적위험도에 따라서도 달라질 수 있다. 따라서, 본 연구에서는 건강한 중년 한국인에서의 포괄적 심혈관건강지표가 이상적인 수준으로 유지되는 기간이 만성신장질환 및 심혈관질환 위험을 예측할 수 있는지 평가하였다.

**연구방법**

이 연구는 지역사회 기반 코호트인 한국인유전체역학조사사업 (KoGES Ansung-Ansan)에 참여한 40-69 세 대상자 중 기반조사에서 만성신장질환이 없었던 7,854 명과 심혈관질환이 없었던 7,796 명을 대상으로 하였다. 이상적 심혈관건강지표는 체질량지수, 혈압, 공복혈당, 총콜레스테롤, 흡연, 음주, 신체활동 수준에 따라 정의되었다.

Cox 비례위험모형을 시행하여 이상적 심혈관건강지표 지속기간과 만성신장질환 및 심혈관질환 발생 위험도의 관련성을 평가하였다.

**연구결과**

기반조사에서의 참가자 평균 연령은 50.0 세였고 47.9%는 남성이었다. 중앙값 기준 15.0 년의 추적조사 기간 동안 1,401 건의 만성신장질환과 493 건의 심혈관질환이 관찰되었다. 이상적 심혈관건강지표 유지기간이 5 년 미만인 군에 비하여, 5–10 년 군의 만성신장질환 상대위험도는 0.63 (95% 신뢰구간 0.39–0.93), 10 년 이상 군의 상대위험도는 0.33 (95% 신뢰구간 0.15–0.74)이었다. 마찬가지로 심혈관건강지표 유지기간 5 년 미만 군에 비하여, 유지기간이 5–10 년 군의 심혈관질환 상대위험도는 0.83 (95% 신뢰구간 0.54–1.27), 10 년 이상 군의 상대위험도는 0.22 (95% 신뢰구간 0.08–0.60)이었으며, 심혈관질환 중에서 특히 관상동맥질환 및 뇌혈관질환 위험도와 강한 관련성이 관찰되었다.

**결론**

한국 성인에서 심혈관건강지표가 이상적인 수준으로 유지되는 기간이 길수록 만성신장질환 및 심혈관질환 발생위험도가 유의하게 낮아지는 경향이 관찰되었다. 중년기에서의 적극적인 생활습관개선과 약물치료로 심혈관건강지표를 이상적 수준으로 오래 유지하는 것이 심혈관질환의 질병 부담 경감에 도움이 될 것이다.