



## Brief Communication

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# Cohort Profile: The Cardiovascular and Metabolic Diseases Etiology Research Center Cohort in Korea

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Mortalities from cardiovascular disease in Korea have decreased markedly over the past three decades. The major cardiovascular and metabolic risk factors, however, remain prevalent, and their burden on health is large. The Cardiovascular and Metabolic Diseases Etiology Research Center (CMERC) planned a cohort study in order to identify novel risk factors and to develop evidence-based prevention strategies of cardiovascular and metabolic diseases. The CMERC deliberately designed two prospective cohorts, a community-based general population cohort (the CMERC cohort) and its sister cohort (a hospital-based high-risk patient cohort), covering a broad spectrum of cardiovascular and metabolic diseases. This paper describes the CMERC cohort study of community-dwelling adults aged 30 to 64 years. A total of 8097 adults completed baseline measurement between 2013 and 2018. Baseline measurements assessed socio-demographic factors, medical history, health-related behaviors, psychological health, social network and support, anthropometry, body composition, and resting blood pressure and comprised electrocardiography, carotid artery ultrasonography, fasting blood analysis, and urinalysis. Both active follow-up through an annual telephone survey and a 5-year on-site health examination survey and passive follow-up through secondary data linkage with national databases, such as national death records, have been applied. Researchers interested in collaborative research may contact the corresponding author.

**Key Words:** Cohort studies, cardiovascular diseases, metabolic diseases, adult, Republic of Korea

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Cardiovascular and metabolic diseases (CVMD) are major causes of death and disability worldwide. Although cardiovascular disease mortality has decreased globally, the absolute number of deaths has increased in most regions of the world. Fortunately, risk factors causally associated with CVMD are widely known, and CVMD can be prevented through lifestyle modifications and existing risk management.<sup>1,2</sup> Notwithstanding, distributions of risk factors, their impact on disease development, the prevalence of disease, and societal health determinants can vary according to regional, racial, cultural, and

economic status,<sup>3-5</sup> which still need studies in various settings. The Cardiovascular and Metabolic Diseases Etiology Research Center (CMERC) planned a new cohort study in order to identify novel risk factors and to develop evidence-based prevention strategies of CVMD in Korea. We have designed two prospective cohorts, a community-based general population cohort (the CMERC cohort) and a hospital-based high-risk patient cohort (the CMERC-HI cohort).<sup>6</sup> This paper focuses on the CMERC cohort.

The CMERC cohort comprises community-dwelling adults who were free of cardiovascular diseases. Recruitment of the study participants and data collection were carried out at two research clinics managed by researchers at Yonsei University College of Medicine (YUCM clinic) in Seoul, Korea and at Ajou University School of Medicine (AUSM clinic) in Suwon, Korea. The YUCM clinic enrolled eligible adults from Seoul and the northwest parts of the capital area (Incheon, Goyang, and Gimpo), and the AUSM clinic targeted individuals living in the southern part of the capital area (Suwon, Yongin, and Hwaseong). The participants were recruited through advertisements in local newspapers, ad posters in public areas, and by word-of-mouth from other participants. Cohort enrollment began in December 2013 and ended in March 2018. Adults aged 30 to 64 years who had lived in their current residence for at least 8 months and had no plan to move out of the study area within 2 years and who were able to articulate their intention regarding study participation were eligible. Among them, those who had been diagnosed with myocardial infarction, heart failure, or stroke in their lifetime; had been diagnosed with cancer within the last 2 years; were currently undergoing cancer treatment; were participating in any randomized clinical trials; or were currently pregnant were excluded. This study was scheduled to enroll 800 adults each year at each research clinic over 5 years, resulting in a total of 8000 participants. The study protocols were approved by the institutional review boards of Severance Hospital, Yonsei University Health System, Seoul, Korea (4-2013-0661) and Ajou University Hospital, Suwon, Korea (AJIRB-BMR-SUR-13-272). Written informed consent was obtained from all participants prior to the baseline measurements.

Baseline measurements assessed socio-demographic factors, medical history, health-related behaviors, psychological health, social network and support, anthropometry, and body composition and included cardiovascular examinations, blood analysis, and urinalysis (Table 1). Details on the study protocol have been reported previously.<sup>6</sup> The majority of measurements were conducted for all participants at the two research clinics, although there were some center-specific measurements and additional measurements available for subsamples of the cohort. Among health-related behaviors, physical activity and sleep quality were assessed using the International Physical Activity Questionnaire-Short Form<sup>7</sup> and the Berlin Questionnaire,<sup>8</sup> respectively. Additionally, we included physical

activity intensity and sleep/wake measurements using a three-axis accelerometer (GENEActiv, Activinsights, Kimbolton, Cambridge, UK) for subsamples at the YUCM clinic and collected objective information on daily sleep and physical activity for 7 consecutive days. Dietary intake was assessed using the semi-quantitative food frequency questionnaire, which was developed and validated for dietary assessment of Korean adults in the Korea National Health and Nutrition Examination Survey (KNHANES).<sup>9,10</sup> Among mental health measurements, depressive symptoms and psychological responses to stressful life events were assessed using the Beck Depression Inventory-II<sup>11,12</sup> and the Life Experiences Survey Questionnaire,<sup>13,14</sup> respectively. Cognitive function was measured only for participants aged  $\geq 50$  years using the Mini-Mental State Estimation for dementia screening.<sup>15</sup> For social health assessment, "ego-centric social network" properties and social support were measured using the questionnaire developed for the Korean Social Life, Health, and Aging Project<sup>16</sup>: An ego-centric social network consists of the participant (ego) and his/her social network members (alters). Participants were asked to list social network members and to provide information about their relationship with each network member, each network member's demographic characteristics, the frequency of talking or meeting with each network member, the degree of emotional closeness they feel to each network member, and social interactions between their social network members. Based on this collective information, each participant's network properties were evaluated, including network size, density, content, composition, emotional closeness of alters, volume of contact with alters, and bridging potential. Physical health examinations were performed on the same day as the participant answered the questionnaires. All participants fasted at least 8 hours. Anthropometric measures, body composition, single-arm blood pressure (BP), resting electrocardiography, and carotid artery ultrasonography were measured in common at the two research clinics. Fasting blood and urine samples were obtained, and bioassays were performed at a designated research laboratory. The YUCM clinic additionally performed simultaneous double-arm BP measurements and radial artery applanation tonometry, as well as bioassays for hemostatic, inflammatory, and cardiac markers. Also, the YUMC clinic obtained information on liver fatness and cross-sectional areas of abdominal fat and thigh muscle from quantitative computerized tomography images according to the study protocol. Meanwhile, the AUSM clinic added oral glucose tolerance tests and measurements of adiponectin, C-peptide, heavy metals, and persistent organic pollutants in the blood. We also measured cellular immunity and immunosenescence biomarkers (CD4, CD8, CD28, and IL-6) known to be associated with cardiovascular disease<sup>17</sup> for subsamples of the participants enrolled at both research clinics. Furthermore, we deposited biospecimens (serum, plasma, buffy coat, and urine) to the National Biobank of Korea<sup>18</sup> for future research. All procedures and measurement

**Table 1.** Summary of Variables Collected at Baseline for the CMERC Cohort Study

Classification	Contents	Method
Socio-demographic factors	Sex, age, education, marriage, cohabitation, economic status, occupation	Questionnaire/interview
Medical history	Past history, family history, current medication	Questionnaire/interview
Reproductive factors	Menarche, menopausal status, reproductive history, gestational diabetes and hypertension, oral contraceptive use, hormone replacement therapy	Questionnaire/interview
Health-related behaviors	Smoking, drinking, diet, physical activity, sleep, obstructive sleep apnea risk	Questionnaire/interview
	Physical activity and sleep*	3-D accelerometer
Psychological health	Depression, stressful life events	Questionnaire/self-report
	Cognitive function†	Questionnaire/interview†
Social network analysis	Eco-centric network properties (network size, density, content, composition, emotional closeness of alters, volume of contact with alters, bridging potential)	Questionnaire/interview
Social support	Social support from a spouse or social network member	Questionnaire/interview
Anthropometric measures	Height, weight, circumferences (arm, waist, hip, thigh)	Examination
	Weight at 20 years	Questionnaire/interview
	Heaviest weight in lifetime	Questionnaire/interview
Body composition	Body fat, lean body mass, muscle mass	Examination (bioimpedance)
	Bone mineral density, body composition	Examination
Blood pressure	Single-arm blood pressure	Examination
	Dual-arm blood pressure‡	Examination
Radial artery tonometry	Augmentation index‡	Examination
Electrocardiogram	12-channel electrocardiogram	Examination
Carotid ultrasonography	Carotid intima thickness, plaque, bulb	Examination
Biochemical indicators		
Urine, common items	Proteins, ketones, blood, bilirubin, and nitrates	Laboratory analysis
Blood, common items	CBC, total protein, albumin, glucose, insulin, triglyceride, total cholesterol, HDL-cholesterol, BUN, creatinine, uric acid, AST, ALT, $\gamma$ -GTP, 25-OH vitamin D, hs-CRP, HbA1c	Laboratory analysis
Blood, additional items*	Lipid markers (LDL-cholesterol), hemostatic markers (prothrombin time, activated partial thromboplastin time, factor VII, factor VIII, fibrinogen, D-dimer), inflammatory markers (IL-1 $\alpha$ , IL- $\beta$ 1, IL-6, TNF- $\alpha$ , TNF- $\beta$ , CD40 ligand), cardiac marker (hs-troponin T)	Laboratory analysis*
	Glucose metabolic markers (OGTT, adiponectin, c-peptide), heavy metals (Pb, Cd, Hg), persistent organic pollutants (As, bisphenol A)	Laboratory analysis*
	Immunosenescence biomarkers (CD4, CD8, CD28, CD57, and IL-6)	Laboratory analysis*

CMERC, Cardiovascular and Metabolic Diseases Etiology Research Center; CBC, complete blood count; HDL, high density lipoprotein; BUN, blood urea nitrogen; ALT, alanine aminotransferase; AST, aspartate aminotransferase;  $\gamma$ -GTP, gamma-glutamyl transferase; hs-CRP, high sensitivity C-reactive protein; HbA1c, hemoglobin A1c; LDL, low density lipoprotein; IL, interleukin; TNF, tumor necrosis factor; OGTT, oral glucose tolerance test; Pb, lead; Cd, cadmium; Hg, mercury; As, arsenic.

\*Measured only for a subgroup of participants; †Measured only for participants aged  $\geq 50$  years; ‡Measured only at Yonsei University College of Medicine clinic.

were performed by trained research staff according to a pre-determined protocol. The equipment used at each clinic was the same wherever possible, although some equipment did vary. To overcome possible measurement errors, we strictly followed a predefined protocol including all aspects of the examination, other than those related to the equipment, such as the participant's position during the test, the measurement site, and the criteria for reading results. We also performed annual self-audits and regularly evaluated the inter-rater reliability of carotid intima-media thickness.<sup>19</sup>

A total of 8097 subjects (4060 in the YUCM clinic and 4037 in the AUSM clinic) were enrolled and completed the baseline examination survey (Table 2). In total, 65.3% of the participants were women. Mean ages were 50.7 years for men and 51.8 years for women. Men reported fewer healthy behaviors,

a smaller social network size, and higher prevalences of cardio-metabolic risk, such as obesity, hypertension, diabetes, and dyslipidemia, compared to women.

The cohort has been followed up using both active (telephone survey and on-site follow-up examination) and passive (data linkage with secondary data sources) strategies. The annual telephone surveys are designed to collect information on changes in health status (new disease diagnosis or death), medical utilization (emergency room visits or hospitalization), and current contact information, and are still ongoing. The response rates remain quite high (Table 3). On-site follow-up health examination surveys are to be conducted at 5-year intervals after the baseline measurement. We are currently conducting the first on-site follow-up examination for the participants enrolled during the first study year: as of mid-

**Table 2.** Distribution of Selected Baseline Characteristics in the CMERC Cohort

Variables	Total (n=8097)	Men (n=2808)	Women (n=5289)
<b>Socio-demographic factors</b>			
Age (yr)	51.4±8.7	50.7±9.3	51.8±8.3
Marriage, married and living with a spouse	7057 (87.2)	2598 (92.5)	4459 (84.3)
Monthly income (10000 won)	500 (333–700)	500 (400–800)	500 (300–700)
<b>Health-related behaviors</b>			
Current smoking	1060 (13.1)	923 (32.9)	137 (2.6)
Current drinking (≥1 unit/month)	4433 (54.8)	2180 (77.6)	2253 (42.6)
Regular walking (≥30 minutes/day)	3747 (46.3)	1321 (47.1)	2426 (45.9)
Energy intake (kcal)	2283.2±808.9	2637.4±897.2	2089.9±683.0
Sleep duration (hr)	6.8±1.2	6.9±1.1	6.8±1.2
<b>Social network proprieties</b>			
Network size (n, 0–6)	3.43±1.67	3.22±1.76	3.54±1.61
Proportion of kin within a network	0.50±0.35	0.47±0.36	0.52±0.34
Proportion of cohabitants within a network	0.39±0.30	0.46±0.33	0.36±0.28
Average closeness to alters (score, 1–4)	3.16±0.61	3.20±0.61	3.13±0.61
Overall volume of contact (days/year)	605.5±331.6	583.5±317.6	617.2±338.2
Network density	0.66±0.28	0.67±0.28	0.65±0.28
<b>Anthropometrics</b>			
Height (cm)	162.1±8.2	170.5±6.0	157.6±5.2
Weight (kg)	63.6±11.1	73.0±10.1	58.6±7.9
Body mass index (kg/m <sup>2</sup> )	24.1±3.1	25.1±2.9	23.6±3.0
Waist circumference (cm)	82.3±9.1	87.6±7.9	79.4±8.4
Total body fat (%)	30.1±7.2	24.4±5.7	33.2±6.0
<b>Cardiometabolic disease status</b>			
Obesity*	2860 (35.3)	1383 (49.3)	1477 (27.9)
Hypertension <sup>†</sup>	2047 (25.3)	961 (34.2)	1086 (20.5)
Diabetes mellitus <sup>‡</sup>	612 (7.6)	320 (11.4)	292 (5.5)
Hypercholesterolemia <sup>§</sup>	1719 (21.3)	507 (18.1)	1212 (22.9)
Hypertriglyceridemia <sup>  </sup>	1854 (22.9)	829 (29.5)	1025 (19.4)
Low HDL cholesterol <sup>¶</sup>	823 (10.2)	520 (18.5)	303 (5.7)
Carotid intima-media thickness (mm)			
Right	0.630±0.123	0.647±0.132	0.622±0.117
Left	0.636±0.137	0.654±0.134	0.627±0.138
<b>Fasting blood analysis</b>			
Glucose (mg/dL)	95.5±20.5	99.8±23.8	93.2±18.1
HbA1c (%)	5.7±0.7	5.8±0.8	5.7±0.6
Insulin (uIU/mL)	9.2±3.9	9.6±4.4	9.0±3.6
Triglyceride (mg/dL)	131.6±92.9	161.4±24.3	115.8±65.6
Total cholesterol (mg/dL)	195.1±34.7	192.9±34.4	196.3±34.8
HDL-cholesterol (mg/dL)	55.9±14.1	49.9±12.3	59.1±13.9
BUN (mg/dL)	14.6±3.8	15.2±3.8	14.3±3.7
Creatinine (mg/dL)	0.9±0.2	1.0±0.2	0.8±0.1
Uric acid (mg/dL)	4.9±1.3	5.9±1.2	4.3±0.9
AST (IU/L)	25.7±13.3	27.4±10.3	24.8±14.6
ALT (IU/L)	25.1±18.4	30.6±19.6	22.1±17.0
γ-GTP (IU/L)	31.1±42.7	47.1±55.9	22.5±30.3
CRP (mg/L)	1.4±4.0	1.7±4.8	1.2±3.5
25-(OH) vitamin D (ng/mL)	16.3±8.6	15.8±6.9	16.5±9.3

CMERC, Cardiovascular and Metabolic Diseases Etiology Research Center; HDL, high-density lipoprotein; HbA1c, hemoglobin A1c; BUN, blood urea nitrogen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GTP, gamma-glutamyl transferase; CRP, C-reactive protein.

Values are presented as a mean±standard deviation, median (interquartile range), or n (%).

\*Obesity was defined as a body mass index ≥25.0 kg/m<sup>2</sup>; <sup>†</sup>Hypertension was defined as either a systolic or a diastolic blood pressure ≥140 mm Hg or ≥90 mm Hg, or when participants self-reported antihypertensive drug treatment; <sup>‡</sup>Diabetes was defined as either a fasting glucose level ≥126 mg/dL or when participants self-reported anti-diabetic treatment, such as taking a hypoglycemic agent or insulin; <sup>§</sup>Hypercholesterolemia was defined as either a serum cholesterol level ≥240 mg/dL or when participants self-reported lipid-lowering drug treatment; <sup>||</sup>Hypertriglyceridemia was defined as either a serum triacylglycerol level ≥200 mg/dL or when participants self-reported lipid-lowering drug treatment; <sup>¶</sup>Low HDL cholesterol was defined as an HDL cholesterol level <40 mg/dL.

**Table 3.** Numbers and Response Rates of Annual Telephone Follow-Up Surveys

Enrollment		Annual telephone follow up			
Period	n	1st	2nd	3rd	4th
2013–2014	1608	1603 (99.7)*	1594 (99.1)	1576 (98.0)	1565 (97.3)
2014–2015	1623	1616 (99.6)	1611 (99.3)	1602 (98.7)	-
2015–2016	1658	1651 (99.6)	1640 (98.9)	-	-
2016–2017	1665	1660 (99.7)	-	-	-
2017–2018	1543	-	-	-	-
Total	8097	6530 (99.6) <sup>†</sup>	4845 (99.1) <sup>†</sup>	3178 (98.4) <sup>†</sup>	1565 (97.3) <sup>†</sup>

Values are presented as n (%).

\*Means the proportion of followed cases among enrolled cases of each period; <sup>†</sup>Means the proportion followed cases for each follow-up time.

May 2019, 500 participants completed the on-site follow-up survey. For passive follow-up, the CMERC obtained written consent to use personal information for secondary data linkage from each participant. We recently linked CMERC cohort information with the national death registry maintained by Statistics Korea. Among participants enrolled in the first three years who agreed to data linkage (n=4889), four deaths were officially identified through December 31, 2016, which was consistent with the results from the annual telephone surveys. Regular data-linkage updates and passive follow-up using other data sources, such as the National Health Insurance Claims database and the National Health Screening database, will be performed.

As the CMERC cohort has only recently completed the baseline examinations of study participants, the findings published so far primarily cover the study methodologies or the results of cross-sectional analysis of the baseline data.<sup>6,19-32</sup> Several studies using this cohort are currently either ongoing or being processed for publication. Some of the key findings are as follows: We compared low density lipoprotein (LDL)-cholesterol estimations using various formulas with direct measurement of LDL-cholesterol<sup>20</sup> and found that the accuracies of the formulas were differed considerably according to triglycerides levels. We also found large inter-arm differences in BP in a small portion of study participants and that high systolic BP, chronic inflammation, and obesity were associated with larger differences in inter-arm BP.<sup>21</sup> Meanwhile, although a positive association between glycosylated hemoglobin (HbA1c) and estimated average glucose levels is widely known, there has been no study thereof targeting the Korean population. Indeed, we found an apparent association between HbA1c level and mean blood glucose level.<sup>22</sup> Visceral fat mass measured using dual-energy X-ray absorptiometry was found to be a stronger indicator of diabetes and prediabetes than other anthropometric obesity indices.<sup>23</sup> Other reports describe novel biomarkers for exposure to environmental pollutants, inflammation, and immune-mediated aging processes.<sup>24-32</sup> We have reported on the potential impact of cadmium exposure on an association between inflammation generated

by lipopolysaccharides and metabolic syndrome,<sup>24</sup> an independent association between bisphenol A exposure and systemic inflammation,<sup>25</sup> and a positive association between blood mercury concentration and visceral adipose tissue content.<sup>26</sup> While it is known that T cells play a role in the development of coronary artery diseases (CADs), it remains unclear which type of T cells are responsible for the pathogenesis. We found that senescent CD8<sup>+</sup> T cells might be associated with the pathogenesis of CAD through their pro-inflammatory and highly cytotoxic capacities.<sup>31</sup> In another study, we suggested that immune dysfunction mediated by the key uremic toxin, indoxyl sulphate, may provoke endothelial damage in patients with end-stage renal disease, thereby elevating the risk of cardiovascular disease.<sup>32</sup>

The CMERC cohort study has several strengths and weaknesses. The important strength is its plethora of information, including emerging risk factors and biomarkers, as well as well-established traditional risk factors, of CVMD, along with bio-specimens for future research. Among the emerging risk factors measured, social network characteristics and immunosenescent biomarkers are particularly unique. While social environments have been deemed to have a major influence on both the adoption of health behaviors and the health status of adults, the relationships between social support networks and health have not been well studied. Increasing evidence supports that immunosenescence may play some role in the development and progression of chronic degenerative disease; however, the underlying mechanisms are still unclear. Another strength is the study design. The CMERC cohort of community-dwelling participants and the CMERC-HI cohort of high-risk patients comprise measurements of many risk factors using the same methods. Thus, the two sister cohorts covering a broad spectrum of CVMD enables us to conduct primary and secondary prevention studies. The CMERC cohort has weaknesses, however, that should be considered. The main weakness is the limited generalizability that often occurs in cohort studies. The study population was not randomly drawn from the entire target population, which needs to be considered when applying the results to the target population. Another limitation is that some measurements were performed using different equipment available at each research clinic. Nevertheless, this drawback is confined to examinations that require particularly expensive equipment, such as imaging studies, and we have made efforts to avoid measurement errors due to reasons other than the equipment, such as the operator or the patient's position during the measurement.

The baseline measurement data and bio-specimens of the CMERC cohort have been deposited at the National Biobank of Korea managed by the Korea National Institute of Health (KNIH). Currently, access to the data is limited to researchers, but will soon be open to others. Further information is available on the KNIH website (<http://www.nih.go.kr/index.es?sid=a5>). Individuals can gain access to the dataset after receiving ap-



proval from the research proposal committee of the KNIH. Also, researchers interested in collaborative research can contact the CMERC principal investigator, Hyeon Chang Kim, at hckim@yuhs.ac.

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## AUTHOR CONTRIBUTIONS

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