

# BMJ Open Health and Prevention Enhancement (H-PEACE): a retrospective, population-based cohort study conducted at the Seoul National University Hospital Gangnam Center, Korea

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## ABSTRACT

**Purpose** The Health and Prevention Enhancement (H-PEACE) study was designed to investigate the association of diagnostic imaging results, biomarkers and the predisease stage of non-communicable diseases (NCDs), such as malignancies and metabolic diseases, in an average-risk population in Korea.

**Participants** This study enrolled a large-scale retrospective cohort at the Healthcare System Gangnam Center, Seoul National University Hospital, from October 2003 to December 2014.

**Findings to date** The baseline and follow-up information collected in the predisease stage of NCDs allows for evaluation of an individual's potential NCD risk, which is necessary for establishing personalised prevention strategies. A total of 91 336 health examinees were included in the cohort, and we repeatedly measured and collected information for 50.9% (n=46 484) of the cohort members. All participants completed structured questionnaires (lifestyle, medical history, mini-dietary assessment index, sex-specific variables and psychiatric assessment), doctors' physical examinations, laboratory blood and urine tests and digital chest X-ray imaging. For participants with available data, we also obtained information on specific diagnostic variables using advanced diagnostic tests, including coronary CT for coronary calcium scores, colonoscopy and brain MRI. Furthermore, 17 455 of the participants who provided informed consent and donated blood samples were enrolled into the Gene-environmental interaction and phenotype study, a subcohort of the H-PEACE, from October 2013, and we analysed genome-wide single-nucleotide polymorphism array data for 6579 of these blood samples.

**Future plans** The data obtained from this cohort will be used to facilitate advanced and accurate diagnostic techniques related to NCDs while considering various phenotypes. Potential collaborators can access the dataset after receiving approval from our institutional review board. Applications can be submitted on the study homepage (<http://en-healthcare.snuh.org/HPEACEstudy>).

## Strengths and limitations of this study

- The strengths of the Health and Prevention Enhancement study include a large number of healthy subjects (n=91 336 healthy examinees, from the Healthcare System Gangnam Center, Seoul National University Hospital, between 2003 and 2014) and a structured and organised database.
- This study not only includes data widely used in medical check-ups but also data from sophisticated high-quality advanced examinations to investigate clinical effectiveness in predicting the predisease stage of non-communicable diseases, including malignancies and metabolic diseases, in an average-risk population in Korea.
- Another strength includes the active and passive follow-ups and the ability to obtain complete data, including deaths and incidental cancer cases, even among those who discontinued visiting our centre.
- The data from this study will allow us to contribute to active, effective prevention of the development of cancers and non-communicable diseases.
- The major weakness of this cohort is that it may show selection bias because only subjects who voluntarily visited our centre were included in the study.

## INTRODUCTION

In recent decades, the prevalence of non-communicable diseases (NCDs), such as malignancy, metabolic disease and cardiovascular disease, has rapidly increased in Korea.<sup>1 2</sup> To address this problem, a comprehensive approach that accounts for lifestyle, environmental factors and genetic variability is needed as NCDs are known to be caused by both genetic and environmental factors.<sup>3 4</sup> Precision medicine is emerging as a potential solution.<sup>5 6</sup> This type of medicine categorises individuals into different subgroups based on their susceptibility to disease and then focuses

on individuals in whom interventions will be helpful.<sup>7</sup> One of the major components of efficient prevention and early detection of NCDs is thus identifying high-risk populations among those in a predisease or asymptomatic stage.

The Seoul National University Hospital (SNUH) Healthcare System Gangnam Center provides comprehensive medical check-ups and screening, and nearly 20 000 people visit this centre each year. A data warehouse, HEALTH-WATCH, was built as a prototype database for this cohort study within the healthcare research institute from the start of the centre in 2003.<sup>8</sup> Using HEALTH-WATCH, we have published many articles that have primarily been focused on cancer screening and metabolic diseases.<sup>8–19</sup> In 2013, we reorganised the cohorts to support our research and started collecting blood samples to analyse the genetic factors involved in NCDs. We then summarised and integrated our clinical and genetic data in the Health and Prevention Enhancement (H-PEACE) study.

The H-PEACE study was designed to investigate the predisease stage of NCDs, which helps us assess an individual's risk of NCDs and establish personalised prevention strategies. Through analyses of longitudinal data from comprehensive questionnaires and clinical and laboratory tests, the H-PEACE study can expand our knowledge of NCD prevention, as well as our knowledge of high-risk populations, to improve the early detection of NCDs. The findings can inform treatment priorities and therapeutic guidelines related to NCDs. Finally, the H-PEACE study can contribute to enhancing public health and improving quality of life.

## COHORT DESCRIPTION

### Participants

The H-PEACE study collected data from 91 336 Koreans aged  $45.5 \pm 11.7$  years (50 507 men and 40 829 women) who received a health check-up between October 2003 and December 2014 at the SNUH Gangnam Center (IRB no. H-1311-031-531). We prospectively collected blood samples from 17 455 of those individuals (9396 men and 8059 women) from October 2013 to form the Gene-environmental interaction and phenotype (GENIE) study, a subcohort of the H-PEACE study. Furthermore, we obtained data for genome-wide single-nucleotide polymorphism (SNP) arrays using 6579 donated blood samples. The flow chart of the H-PEACE study subjects is illustrated in [figure 1](#), and the distribution of the participants in Korea in [figure 2](#).

### Repeated measurement and active and passive follow-up

Annual health exams are mandatory for all workers under the Industrial and Safety Law in Korea. In the H-PEACE study, there are two follow-up systems (passive and active follow-up system) for tracking the development of the new diseases and death of the participants. We have annually updated the survival data by linking to National

Death Certificates through requests to Statistics Korea. Under the passive follow-up systems, >99% of participants are followed up for their new cancer development and death annually.

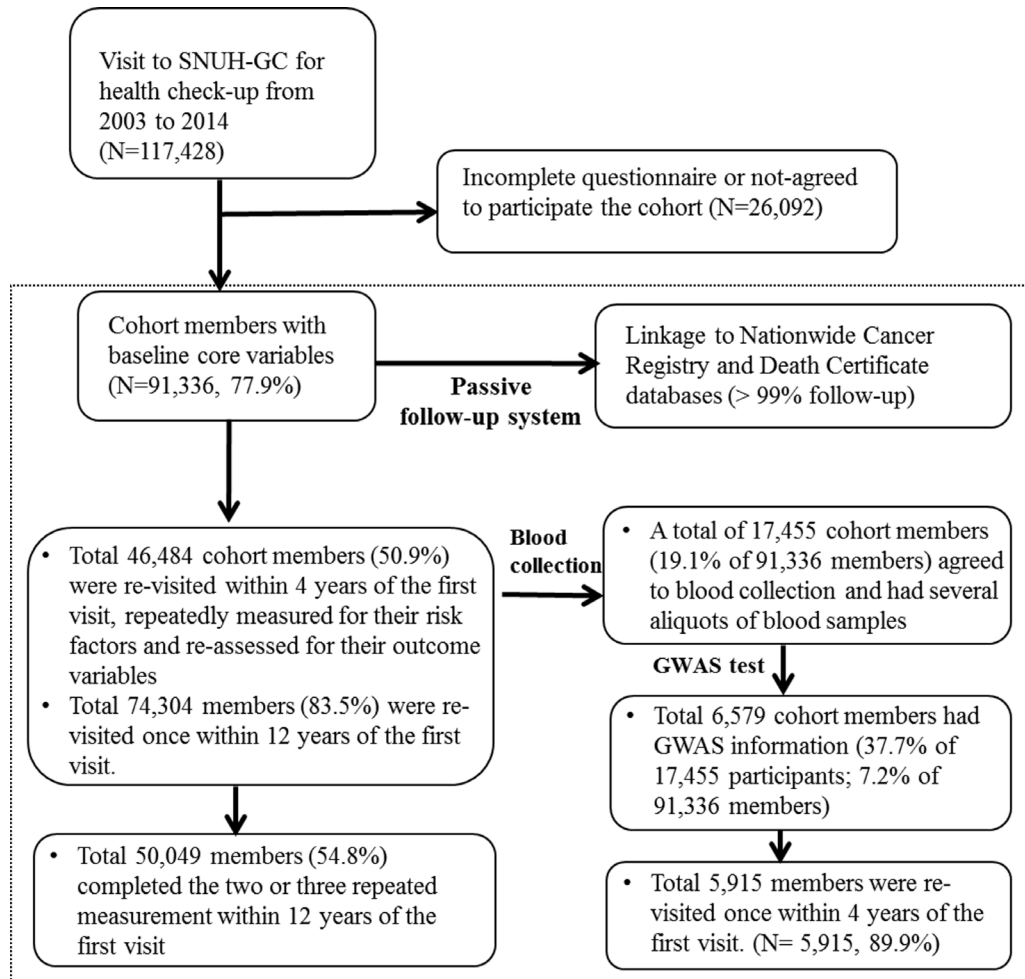
Moreover, the study participants are followed up for their new disease status by revisit to centre for repeated measurement and assessment system. This active follow-up system allows the subject to voluntarily visit our centre. The health check-up system in Korea has two systems in which the National Health Insurance Corporation (NHIC) pays for participants' basic health examination fee once every two years or in which the health examination participants pay all expenses for their health examination fees. The latter programme includes more precise health examination testing that individuals want, and all costs must be paid by individuals. We are under the latter system, and the health examination participants have to pay for all the health check-ups under their voluntary visit. The participants who have undergone health examinations at our centre may receive health check-ups afterwards at different centres that are under partial coverage of the NHIC without revisiting our centre. Although the health check-up services conducted in our centre include a variety of tests that the subject wants, including the basic health check-up programme conducted by the NHIC, we have to make a lot of effort in order for the subject to return to our centre because the former health check-up system covered by the NHIC is free-paid for the basic health check-up programme. We are using a number of ways to encourage their return to our centre. To encourage participants, we provide reminder calls every year and send healthcare information about people's next health check-up date via phone and letter. So the eligibility for follow-up assessment depends on the participants' voluntary revisit need and self-payment availability.

Under this active follow-up system, we did a repeated measurement of risk factors and an assessment of outcome variables for 46 484 individuals (50.9%) of total 91 336 cohort members who participated in the baseline health check-up once within 4 years from the first visit and 74 304 individuals (83.5%) were actively followed up once within 10 years from the first visit. Moreover, 50 049 participants (54.8%) completed the two or three repeated measurements ([figure 1](#)). The median follow-up was 4.04 years (IQR 2.1–6.5).

Of 91 336 cohort members, a total of 17 455 members (19.1%) agreed to blood collection and had several aliquots of blood specimens. Of 17 455 members, 6579 participants were included in the GENIE study with genome-wide association study (GWAS) information (37.7%), and of them, 5915 participants (89.9%) completed at least first follow-up test within 4 years of the first visit. The median follow-up of the GENIE study was 5.23 years (IQR 2.7–8.0).

### Data collection

The H-PEACE study consists of core and specific variables ([tables 1 and 2](#)). The core variables were tests performed



**Figure 1** Study flow diagram of the Health and Prevention Enhancement study. GC, Gangnam Center; GWAS, genome-wide association study; SNUH, Seoul National University Hospital.

in all of the enrolled participants at the regular health check-ups. The specific variables were the tests selectively performed in the participants on request or based on the recommendation of their medical provider according to the participant's symptoms or disease risk factors. These tests were sophisticated and expensive tests that are rarely used in other cohort profiles. In [table 3](#), we describe the representative test for each variable and its participation rate. The tests performed for the covariables and specific variables are described below. All data were collected as part of the comprehensive health check-ups. The flow diagram of health check-ups in our study is illustrated in [figure 3](#). All study protocols are available on request at our homepage (<http://en-healthcare.snuh.org/HPEACEstudy>).

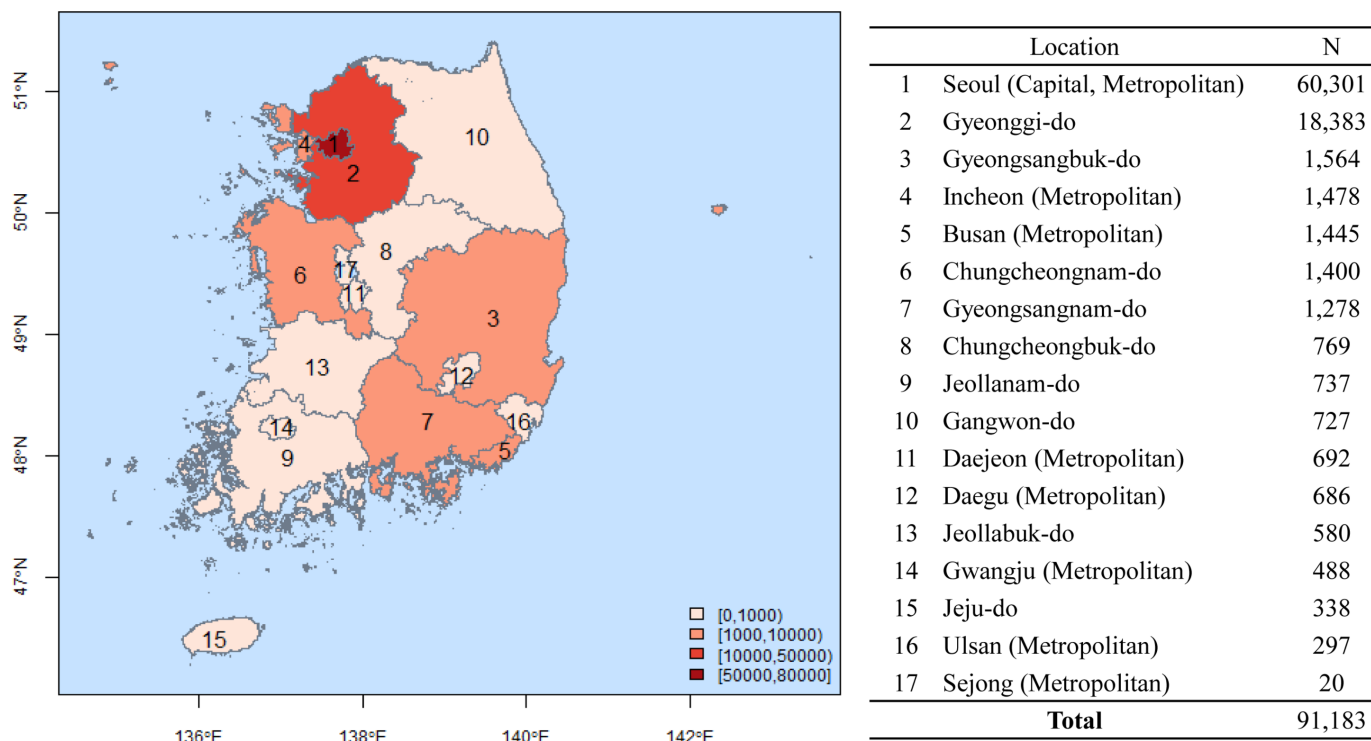
#### Structured questionnaires

Self-reported questionnaires were used to obtain socio-demographic data, personal and familial medical history, health-related behaviours (such as smoking status, alcohol consumption, physical activity, dietary behaviour), International Prostate Symptom Score, female reproductive factors and psychological status. Physical activity levels were assessed using the validated Korean version of

the International Physical Activity Questionnaire short form and were classified into three categories: inactive, minimally active and health-enhancing physically active (HEPA).<sup>20 21</sup> Dietary habits were evaluated using the Mini-Dietary Assessment Index, which was validated in Korean.<sup>22</sup> Psychological status was assessed by the Beck Depression Inventory or Quick Inventory of Depressive Symptomatology-Self Report.<sup>23</sup>

#### Physical examinations

Blood pressure was measured using sphygmomanometers with patients in a seated position after a resting period. If systolic blood pressure was  $\geq 140$  mm Hg or diastolic blood pressure was  $\geq 90$  mm Hg after a rest period and two measurements, we recorded the values and calculated their averages. Height (cm), weight (kg), waist circumference (cm) and body fat composition (%) were measured by trained nurses with participants wearing a lightweight hospital gown and in bare feet. Height and weight were measured using digital scales in a standing position. Waist circumference was obtained by measuring the smallest natural waist circumference area, which is around the umbilicus using a non-stretch tape measure, without any pressure to the body surface during measurements.



**Figure 2** Regional distribution of the Health and Prevention Enhancement study in Korea.

Percentage of body fat and visceral fat area were estimated with a multifrequency bioimpedance analyser with eight-point tactile electrodes (Inbody 720, Biospace, Seoul, Korea). Comprehensive eye examinations (visual acuity, ocular tonometry, slit-lamp test, fundus photography) and hearing tests were also performed.

#### Laboratory tests

Blood samples from the antecubital vein were collected after at least 10 hours of fasting. The blood parameters assessed included complete blood cell count, fasting blood glucose, glycated haemoglobin, uric acid, blood urea nitrogen, creatinine, total calcium, inorganic phosphorus, glucose, sodium, potassium, chloride, total CO<sub>2</sub>, total protein, albumin, total bilirubin, aspartate transaminase, alanine transaminase, gamma-glutamyl transferase, total cholesterol, low-density lipid cholesterol, high-density lipid cholesterol, triglycerides, high-sensitivity C reactive protein concentration, prothrombin time, activated partial thromboplastin time, hepatitis B surface antigen, anti-HBs, HAV Ab IgG, alpha-fetoprotein, cancer antigen 19-9, carcinoembryonic antigen and prostate-specific antigen in men and cancer antigen 125 in women. The laboratory medicine department at the SNUH has been certified by the Korean Society of Laboratory Medicine and participated in the College of American Pathologist's Survey/Proficiency Testing programme. Urine tests were performed by stick test using spot urine. Semiquantitative variables included pH, protein, glucose, ketone, bilirubin and blood. Stool samples were collected to conduct faecal occult blood tests and parasite assays.

#### Digital imaging and specific diagnostic variables

Chest X-ray was included as a core variable of the H-PEACE study, which included specific information on diagnostic variables (table 1). First, the GENIE study collected donated blood samples from 17 455 recipients, and genome-wide SNP arrays from 6579 donated blood samples have already been analysed using the Affymetrix platform (Axiom Customized Genome-Wide Human Assay) (table 3). We plan to increase the available genetic information by 2020 using an SNP array. The PLINK program V.1.9 and R statistics V.3.3.0 were used for quality control procedures and data analysis. SNP genotype data combined with clinical data from the H-PEACE study were used to evaluate gene-environment interactions and to define the related phenotypes.

In total, 12 846 participants underwent coronary CT with a coronary calcium score to assess coronary calcification. The calcium score of the coronary artery is a strong predictor of myocardial infarction and sudden cardiac death.<sup>24</sup> In addition, 34 771 participants underwent visceral fat CT to measure visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT). The detailed methods used to measure VAT area and SAT area on abdominal fat CT images have been described elsewhere.<sup>17</sup> This quantitative assessment of intra-abdominal adipose tissue is considered the gold standard for measuring the amount of visceral fat.<sup>25</sup> With advanced imaging techniques including echocardiography, brain MRI/magnetic resonance angiogram, carotid Doppler ultrasound, abdominal ultrasonography and abdominal CT, we elucidated the correlation of visceral obesity

**Table 3** Participation rate for the core and specific variables collected in the Health and Prevention Enhancement (H-PEACE) study at baseline

Variables	Study participants (N)	Participation rate (%)*
<b>Core variables</b>		
Most core variables	≥90 377	≥99
ECG	91 197	99.8
Estimated GFR	91 197	99.8
Stool parasite examination	82 493	90.3
<i>Helicobacter pylori</i> IgG Ab	81 142	88.8
Thyroid function test	77 313	84.6
CLO test or UBT test for current <i>H. pylori</i> infection	67 986	74.4
Gastroendoscopy with pathological report	66 451	72.8
<b>Specific variables</b>		
Dental examination	43 232	47.3
Colonoscopy with pathological reports	46 050	50.4
Abdomen CT with visceral fat CT	34 771	38.1
Abdomen sonography	33 446	36.6
Echocardiography	20 688	22.7
Coronary CT	12 846	14.1
Echocardiography, treadmill test	9910	10.9
SNP from GWAS	6579	7.2
Bone densitometry (postmenopausal females)	26 376	99.4
E2 levels (postmenopausal females after 5 years from menopause)	4742	49.9
Bone densitometry (men≥50 years)	9488	48.9
T levels (men≥60 years)	6697	52.9
HPV genotyping (females)	12 999	31.8
Pap smear (women≥35 years)	12 951	49.1
<b>Blood collection for the GENIE study</b>		
SNP variations in the GWAS	6579	37.7†

\*Participation rate of all 91 336 H-PEACE cohort members.

†Participation rate of all 17 455 GENIE study members (a subcohort of the H-PEACE study).

CLO, *Campylobacter*-like organism; GENIE, Gene-environmental interaction and phenotype; GFR, glomerular filtration rate; GWAS, genome-wide association study; HPV, human papillomavirus; SNP, single-nucleotide polymorphism; UBT, urea breath test.

with vascular disease using both data in a complementary manner. The core variables of the H-PEACE study including the blood test results, questionnaire findings and depression scores can contribute to determining

the correlation between visceral obesity and metabolic phenotype.

We collected ECG reports from 91 197 consecutive recipients to evaluate the incidence and risk factors of atrial fibrillation, a significant risk factor for stroke. The effects of a bundle branch block or atrioventricular block on stroke and cardiac disease were also analysed. Furthermore, we collected Holter monitor results to confirm the ECG reports.

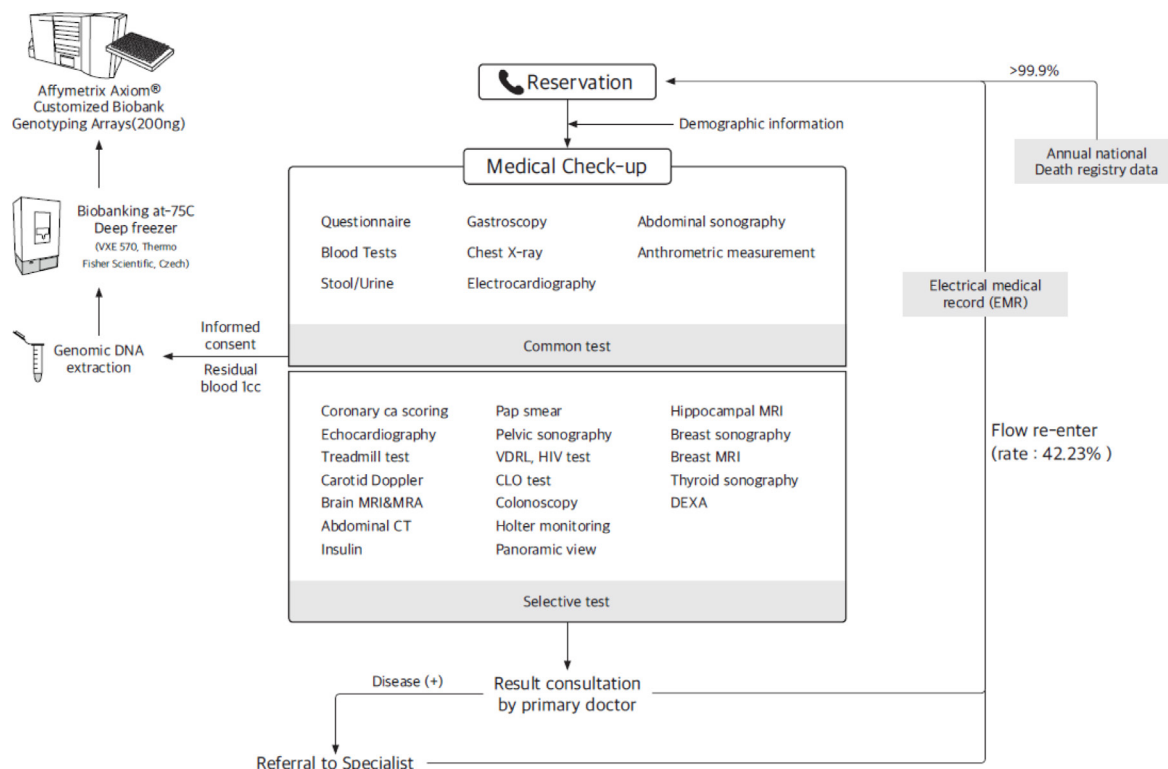
Human papillomavirus (HPV) is known to lead to cervical cancer in women.<sup>26</sup> Of the participants in the H-PEACE study, 12 951 women underwent both a liquid-based cervical cytology (SurePath LBC, Becton Dickinson, Franklin Lakes, New Jersey, USA) and an HPV genotyping test using an HPV DNA chip (MyHPV Chip, Biomedlab, Seoul, Korea) for cervical cancer screening.<sup>27</sup> We also included the results of gynaecological sonography, as well as venereal disease research laboratory and HIV tests.

WHO considers *Helicobacter pylori* infection a class I carcinogen for gastric cancer.<sup>13</sup> The diagnosis of *H. pylori* infection was based on the detection of serum *H. pylori* IgG antibody using a kit (*H. pylori*-EIA-Well, Radim, Rome, Italy) that was previously validated in a nationwide Korean seroepidemiological study.<sup>28</sup> Furthermore, 66 451 recipients had available upper endoscopy data with pathology results. Serum pepsinogen data and eradication history were also collected.

A total of 46 050 participants in the H-PEACE study received a colonoscopy in our centre. All colonoscopies were conducted by board-certified endoscopists, and the average adenoma detection rate in recipients aged 50–70 years was >30%.<sup>12</sup> Endoscopes including the CF-H260 and CF-HQ290 series (Olympus, AIZU, Japan) and the EC-450HL5, EC-450WM5 and EC-590ZW series (Fujinon, Saitama, Japan) were used. Histological diagnoses at our centre were determined according to the WHO classification of tumours of the digestive system.<sup>29 30</sup> All colonoscopy results and corresponding pathology reports were collected.

We calculated estimated glomerular filtration rate (GFR) using the chronic kidney disease epidemiology collaboration equation and the modification of diet in renal disease formula. We collected GFR data successively to identify the risk factors for chronic kidney disease. We also included spot urine sodium and creatinine ratio and 24-hour urine data including GFR.

Dental exams were conducted in 43 232 participants. Periodontitis is highly prevalent among adults and is one of the most common causes of teeth loss after 40 years.<sup>31–33</sup> Furthermore, periodontitis can induce systemic inflammation, as well as masticatory dysfunction and poor nutritional status.<sup>32</sup> This is the first cohort study to include a large number of dental exams to evaluate the progression of periodontitis. In this study, 43 232 participants received a dental exam; 33.1% had mild to moderate periodontitis and 2.1% had severe periodontitis. We also included participants' colonoscopy and coronary CT results, including coronary calcification and colon polyps, to



**Figure 3** Flow diagram of health check-ups in the Health and Prevention Enhancement study. CLO, *Campylobacter*-like organism; DEXA, dual-energy X-ray absorptiometry; MRA, magnetic resonance angiogram; VDRL, venereal disease research laboratory

assess the correlation between periodontitis and systemic inflammation.

The presence of osteoporosis was determined using bone densitometry in 26207 women and 9488 men. We measured bone mineral density (BMD) of the lumbar spine (L1–L4) and femur using dual-energy X-ray absorptiometry (GE Medical, UK). Based on participants' lowest T scores, normal BMD, osteopenia and osteoporosis were defined as T scores of  $-1.0$  SD and above,  $-1.0$  to  $-2.5$  SDs and  $-2.5$  SDs and below, respectively. In this cohort, 26.6% of the participants who underwent bone densitometry were male. Of those, osteopenia was found in 24.75% and osteoporosis was found in 3.21%. The information collected in this cohort also included hormone levels, oestrogen levels in women and testosterone levels in men.

## FINDINGS TO DATE

The baseline characteristics are summarised in table 4, and the morbidity rate of the major outcomes is shown in table 5. The morbidity rates were calculated as the number of findings divided by the number of participants tested. The prevalence of major outcomes (mortality and cancer incidence rate) is provided in table 6. The H-PEACE study has contributed to the research community by publishing >200 articles since the initiation of the data warehouse, HEALTH-WATCH, as a prototype in 2003.<sup>8</sup> Our studies have primarily focused on cancer screening and identifying the risk factors and prognosis of metabolic disease.

For subjects with 1–2 adenomas <10mm in colonoscopy for colon cancer screening, they were classified as a low-risk group having low 5-year colon adenoma incidence rates and were recommended to take further colonoscopic screening test after 5years. For subjects with advanced adenoma, multiple adenoma  $\geq 3$  or larger adenoma sized  $\geq 10$ mm in baseline colonoscopy for colon cancer screening, they were classified as a high-risk group having higher incidence rates of advanced adenoma or higher recurrence rates of adenoma and were recommended to take colonoscopic surveillance at 3years after initial polypectomy.<sup>12</sup> This strategy of colonoscopic surveillance has been reflected in the guidelines for colonoscopic surveillance.<sup>34</sup> In our study, the colonic adenoma incidence rate was 37%. Our centre performed a previous study on the prevalence and risks of colorectal adenoma in asymptomatic Koreans aged 40–49 years undergoing screening colonoscopies.<sup>35</sup> In that study, the prevalence of adenoma was 22.2% in the age group of 40–49years and 32.8% in the age group of 50–59years. This finding is quite consistent with that in our cohort. In the paper, we concluded that the prevalence of adenoma in subjects aged 40–49 years was higher than that in previous studies. Male sex and current smoking habits were among the risk factors.

We also examined the quality of colon cancer screening using metrics such as the adenoma detection rate.<sup>36</sup> Additionally, we evaluated the influence of image-enhanced endoscopy, such as narrow band imaging and Fujinon Intelligent Color Enhancement, using our cohort

**Table 4** Baseline characteristics of the participants in the Health and Prevention Enhancement study

	Total (n=91 336)	Men (n=50 507)	Women (n=40 829)	P values
	n (%)	n (%)	n (%)	
<b>Age (years)</b>				<0.001
<35	16 228 (17.8)	7 666 (15.2)	8 562 (21.0)	
35–44	26 963 (29.5)	15 139 (30.0)	11 824 (29.0)	
45–54	27 915 (30.6)	15 776 (31.2)	12 139 (29.7)	
55–64	14 937 (16.4)	8 717 (17.3)	6 220 (15.2)	
65+	5 293 (5.8)	3 209 (6.4)	2 084 (5.1)	
<b>Sex</b>				
Men	50 509 (55.3)			
Women	40 827 (44.7)			
<b>Cigarette smoking status</b>				<0.001
Non-smokers	48 521 (53.1)	11 779 (23.3)	36 742 (90.0)	
Ex-smokers	22 564 (24.7)	20 469 (40.5)	2 095 (5.1)	
Current smokers	20 251 (22.2)	18 259 (36.2)	1 992 (4.9)	
<b>Regular exercise</b>				<0.001
Inactive	36 343 (39.8)	17 843 (35.3)	18 500 (45.3)	
Minimally active	26 189 (28.7)	16 428 (32.5)	9 761 (23.9)	
HEPA	28 804 (31.5)	16 236 (32.1)	12 568 (30.8)	
<b>Excess alcohol drinking (&gt;140g/week)</b>	20 421 (22.3)	18 934 (37.5)	1 469 (3.6)	<0.001
<b>Education≥high school graduate</b>	78 821 (86.3)	45 538 (90.2)	33 283 (81.5)	<0.001
<b>Hypertension</b>	13 279 (14.5)	9 003 (17.8)	4 276 (10.5)	<0.001
<b>Diabetes</b>	4 377 (4.8)	3 181 (6.3)	1 196 (2.9)	<0.001
<b>Current HBsAg+</b>	3 810 (4.2)	2 377 (4.7)	1 433 (3.5)	<0.001
<b>Current anti-HCV+</b>	887 (0.97)	492 (0.97)	395 (0.97)	0.946
	<b>Mean (SD)</b>	<b>Mean (SD)</b>	<b>Mean (SD)</b>	
<b>Measurements</b>				
Height (cm)	165.6 (11)	171.7 (5.6)	159.9 (5.2)	<0.001
Weight (kg)	64.3 (12.1)	71.5 (9.1)	55.0 (7.2)	<0.001
Body mass index (kg/m <sup>2</sup> )	23.4 (12.1)	24.2 (2.6)	21.5 (2.8)	<0.001
Waist circumference (cm)	83.7 (9.3)	86.5 (7.1)	76.9 (7.5)	<0.001
Skeletal muscle mass (kg)	26.6 (6.0)	30.8 (3.7)	20.6 (2.4)	<0.001
Body fat mass (kg)	26.9 (5.9)	30.8 (3.6)	20.7 (2.3)	<0.001
Visceral fat area (cm <sup>2</sup> )*	79.9 (24.2)	82.3 (23.6)	76.1 (24.7)	<0.001
SBP (mm Hg)	115.4 (15.9)	118.0 (12.2)	111.2 (13.3)	<0.001
DBP (mm Hg)	76.01 (11.9)	79.0 (9.45)	71.36 (9.56)	<0.001
<b>Blood levels</b>				
Fasting blood glucose (mg/dL)	97 (18.6)	100.2 (17.6)	90.7 (16.2)	<0.001
HbA1c (%)	5.56 (0.6)	5.6 (0.6)	5.4 (0.4)	<0.001
Creatinine (mg/dL)	0.84 (0.17)	0.93 (0.13)	0.68 (0.10)	<0.001
Albumin (g/dL)	4.62 (0.25)	4.64 (0.24)	4.58 (0.25)	0.002
Total cholesterol (mg/dL)	191.03 (33.02)	192.5 (33.1)	188.6 (32.8)	0.105
Triglycerides (mg/dL)	101.2 (64.2)	117.9 (68.8)	74.6 (44.9)	<0.001
LDL cholesterol (mg/dL)	119.8 (31.6)	126.3 (31.3)	112.6 (30.0)	<0.001
HDL cholesterol (mg/dL)	54.3 (13.2)	49.4 (9.5)	59.7 (12.6)	<0.001
Hs-CRP (mg/dL)	0.12 (0.26)	0.12 (0.26)	0.10 (0.26)	0.285

\*Visceral fat area is defined here as the cross-sectional area of visceral fat found in the abdomen.

Anti-HCV, anti-hepatitis C antibody; DBP, diastolic blood pressure; HBsAg, hepatitis B surface antigen; HDL, high-density lipid; HEPA, health-enhancing physically active; Hs-CRP, high-sensitivity C reactive protein; LDL, low-density lipid; SBP, systolic blood pressure.

**Table 5** Morbidity rates after active follow-up with specific measurements in the Health and Prevention Enhancement study

Test	Definition	Participants tested N	Follow-up years Median (IQR)	Clinical finding* N	
Coronary calcification	▶ Coronary artery calcium score>400 at coronary CT	12 846	5.6 (3.2–8.0)	805	
Atrial fibrillation	▶ ECG and/or ambulatory ECG	91 076	4.1 (2.1–6.5)	446	
Left bundle branch block	▶ ECG and/or ambulatory ECG	91 076	4.1 (2.1–6.5)	64	
Chronic kidney disease	▶ Estimated GFR†<60mL/min/1.73 m <sup>2</sup>	91 197	4.0 (2.1–6.5)	5372	
Visceral obesity	▶ Men>10000 cm <sup>2</sup> , Women>8000 cm <sup>2</sup> in abdomen visceral fat CT	34 771	5.0 (3.0–7.4)	23 126	
Fatty liver	▶ Abdominal sonography and/or abdominal CT	34 771	5.0 (3.0–7.4)	Mild	10 244
				Moderate	5963
				Severe	688
Abnormal thyroid function	▶ Thyroid hormone measurement	77 313	4.1 (2.2–6.6)	Hypothyroidism	363
				Hyperthyroidism	1260
<i>Helicobacter pylori</i> infection	▶ <i>H. pylori</i> IgG Ab and/or CLO test or UBT test for current <i>H. pylori</i> infection	81 142	4.2 (2.3–6.7)	44 304	
High-risk HPV infection	▶ HPV 16, 18 positive finding in HPV genotyping	12 999	5.0 (3.1–7.2)	1462	
Parasite infection	▶ Stool examination	82 493	4.1 (2.2–6.6)	<i>Clonorchis sinensis</i>	1262
				<i>Ascaris lumbricoides</i>	124
				<i>Trichuris trichiura</i>	256
				<i>Metagonimus yokogawai</i>	412
Premalignant conditions of stomach	▶ Gastroendoscopy with pathological reports	66 451	4.2 (2.3–6.7)	Atrophic gastritis	23 896
				Intestinal metaplasia	10 187
Malignant gastric cancer	▶ Gastroendoscopy with pathological reports	66 451	4.2 (2.3–6.7)	299	
SIL	▶ Pap smear and pathological report	12 951	5.0 (3.1–7.2)	Total SIL	375
				Low grade	315
				High grade	60
Premalignant colonic neoplasms	▶ Colonoscopy with pathological reports	46 746	4.8 (2.9–7.1)	Adenoma	18 656‡
				Serrated polyp	1178‡
				Carcinoid	150
Malignant colon cancer	▶ Colonoscopy with pathological reports	46 746	4.8 (2.9–7.1)	262	
Low bone density	▶ Bone densitometry	35 695	4.8 (2.9–7.2)	Osteopenia	2322
				Male	8279
				Female	
				Osteoporosis	305
				Male	1348
				Female	
Periodontitis	▶ Dental examination	43 232	4.9 (2.8–7.2)	Total periodontitis	15 204
				Mild to moderate	14 292
				Severe	912

\*The number of findings among the participants who were at risk.

†The GFR was estimated by the Chronic Kidney Disease Epidemiology Collaboration equation and the Modification of Diet in Renal Disease formula.

‡Adenoma and serrated polyp detection rate were calculated in participants aged 50–75 years.

CLO, *Campylobacter*-like organism; GFR, glomerular filtration rate; HPV, human papillomavirus; SIL, squamous intraepithelial lesion; UBT, urea breath test.



**Table 6** Major cancer incidence and outcomes based on record linkage to the Nationwide Death Certificate Database in the Health and Prevention Enhancement (H-PEACE) study\*

	Cancer incidence (n)			All-cause death† (n)		
	Total	Men	Women	Total	Men	Women
Total cancer	2814	1402	1412	207	150	57
Thyroid	956	390	566	3	3	0
Stomach	513	337	176	37	29	8
Breast	343	1	342	6	0	6
Colorectal	284	182	102	28	20	8
Lung	186	109	77	45	32	13
Prostate	127	127	0	3	3	0
Kidney	91	71	20	1	1	0
Liver	87	71	16	31	28	3
Gynaecology	52	0	52	7	0	7
Pancreas	42	25	17	27	19	8
Brain	39	20	19	0	0	0
Haematological	39	24	15	5	3	2
Biliary tract	32	26	6	11	9	2
Oesophagus	23	19	4	3	3	0

\*Median (IQR) follow-up years of the 91 336 participants=4.04 (2.13–6.5).

†Since the Nationwide Death Certificate Database does not provide information about cause of death, number of death includes death from not only cancer but also other causes. Among the 91 336 H-PEACE participants, the all-cause mortality rate was 969: 715 men and 254 women.

data.<sup>10 37 38</sup> For gastric cancer screening, the effect of screening endoscopy remains controversial, but population-based screening has been undertaken in Korea and Japan. For participants with intestinal metaplasia in gastroendoscopy, we also classified them into high-risk group and recommended an annual endoscopic screening, based on study results that people with strong risk factors such as male and an older age can quickly find early-staged endoscopically treatable gastric cancer by taking annual gastroendoscopic screening.<sup>11</sup> In our cohort, 54% had *H. pylori* infection and 36% had atrophic gastritis. In a nationwide multicentre study in Korea performed by our centre for the prevalence of *H. pylori* infection, the seropositive rate of *H. pylori* was 59.6%.<sup>39</sup> This rate is quite consistent with our study result and consequently explains the relatively high percentage of atrophic gastritis that we observed. Gastric mucosa-associated lymphoid tissue lymphomas (MALToma) and suspicious MALToma lesions were also detected in screening endoscopies, and the prevalence of gastric MALToma was high in middle-aged women.<sup>40</sup> Active endoscopic screening for gastric cancer had the additional benefit of detecting early-stage MALToma.<sup>40 41</sup> Furthermore, we established that small subepithelial tumours that were incidentally found during upper endoscopy screening showed no size change in subsequent follow-up periods.<sup>37</sup>

Our research focus was not limited to cancer screening. We also examined metabolic diseases such as non-alcoholic fatty liver disease (NAFLD) and metabolic syndrome. Consistent with our results, the population

prevalence of NAFLD in Korea is >25%, like that in many Western countries.<sup>19 42–44</sup> Although subjects in this cohort are relatively young and lean, lean NAFLD (or non-obese NAFLD) is more common in Asians (including Koreans) than in Western populations. Asians generally have a higher percentage of visceral fat and body fat than people of other races of the same age, sex and even body mass index (BMI).<sup>45–47</sup> As visceral obesity is a major risk factor for lean NAFLD, this might have affected the higher prevalence of NAFLD in this cohort, comprising relatively lean subjects.<sup>45</sup> In addition, the term ‘fatty liver’ in this paper includes not only NAFLD but also alcoholic fatty liver disease. The proportion of subjects who drink alcohol heavily in this cohort is as high as 37.5% in men, which might affect the high prevalence of fatty livers that we observe.

We reported that metabolic syndrome was an independent risk factor of silent brain infarction using brain MRI data (OR 2.18; 95% CI 1.38 to 5.82,  $p=0.001$ ).<sup>48</sup> The prevalences of metabolic syndrome and its components were higher in subjects with silent brain infarctions than in those without. This is the first study to demonstrate an association between metabolic syndrome and silent brain infarction. This finding might help identify healthy people at increased risk for developing silent brain infarction. We also found an effect of body fat distribution on the incidence of NAFLD and reflux oesophagitis using abdominal fat CT data.<sup>9 14</sup> We identified a relationship between NAFLD and the risks of coronary heart disease and arterial stiffness based on coronary CT and the

cardio-ankle vascular index (CAVI), respectively.<sup>16–19</sup> To elucidate the relationship between NAFLD and the risk of coronary heart disease, we used the coronary artery calcification score as measured by coronary CT. This measurement showed that patients with NAFLD are at increased risk for coronary atherosclerosis (OR 1.28, 95% CI 1.04 to 1.59,  $p=0.023$ ).<sup>17</sup> In the study on the association between NAFLD and arterial stiffness, we used CAVI, a new measurement of arterial stiffness. In an age-adjusted, sex-adjusted and BMI-adjusted model, NAFLD was associated with a 42% increase in the risk for arterial stiffness, and this increased according to the severity of NAFLD.<sup>16</sup> The effect of physical activity on NAFLD was also demonstrated using data from the questionnaires.<sup>49</sup>

The list and number of publications can be requested on our homepage (<http://en-healthcare.snuh.org/HPEACEstudy>).

### STRENGTHS AND LIMITATIONS

This study has several potential limitations as below. First, our study participants are composed of individuals who voluntarily visited our centre and their data collection for the repeated measurements rely on participants' self-paid. Our system of enrolling cohort members includes a potential selection bias. Second, self-recorded questionnaires are used to obtain the information of risk factors and disease histories before the next visit of study participants to our centre, and this procedure leads to recall bias and response bias. Third, our active follow-up rates in assessing outcome variables and repeatedly measuring risk factors are not high, leading to selection bias. However, since active follow-up rates are increasing every year, at least 87% of follow-up is expected if all subjects are terminated for at least 10-year follow-up. Fourth, in our cohort, we used to measure waist circumference as the definition of the smallest area around the belly button below the rib cage and above the hip bone, although the ideal way is to measure the midway between the top of the hip bone and below the rib cage. The former is usually called the natural waist, and we used this former definition for practical reason to reduce intraindividual measurement bias in waist circumference. In health check-up at our centre, a lot of participants (about 100–120 health examinees) every day visit the centre for health examination and many health technicians and nurses take measurement of waist and hip circumferences. For each participant, there is a very little chance to take measurement of waist at the time of revisit by same nurses met at the time of cohort enrolment. The intraindividual measurement bias in measuring waist circumference may be problematic at our centre and thus we thought that it was necessary to use the most practical and easy waist measurement together with repeated nurse training. We did a small pilot study for measuring waist by the two methods for 10 men and 16 women. The ideal measuring method (midway measurement) has a limit in consuming time and effort due to difficulty in method itself. In spite of short

time and smaller effort in measuring waist, the natural waist measuring method showed an excellent agreement (intraclass correlation coefficients=99% in men and 93% in women) with ideal method and there were no shift between obesity groups classified by each method. Fifth, there is no information of cancer histology subtypes for cohort participants ascertained as new cancer development. Individual cancer development in study participants was ascertained with data linkage to the nationwide cancer registry data. Korea cancer registry data include International Classification of Diseases, Tenth Revision code, T-code (Topography) and M-code (Morphology in primary cancer sites). For example, among the stomach cancer types, 51.3% were adenocarcinomas, 22.1% were tubular adenocarcinomas and only 4.9% were histological NOS.<sup>50</sup> Future studies will attempt to merge the individual data associations of M-code and T-code. Finally, the definition of a disease status could be changed during the follow-up periods as new guidelines are declared. For instance, guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults opened at November 2017<sup>51</sup> recommending a new definition for hypertension. This paper was written before the declaration was done. We have the raw data of blood pressure and the definition can be applied to the study population. But for those who had already been under antihypertensive medication at the point of enrolment in our cohort, they had followed the previous guidelines for indication of treatment. This makes it difficult to reclassify these patients according to the new guidelines. In the future follow-up period, we will pay close attention to clearly declare the definition of disease we are applying according to the period of terms.

A major strength of the H-PEACE study is its structured and organised database, which not only includes data widely used in medical check-ups but also data from sophisticated high-quality advanced examinations, such as colonoscopy, brain MRI, abdominal CT and abdominal fat CT. Particularly in our study, comprehensive biomarkers related to NCDs, including cancer antigens and infection markers, were included, which have not been included in the medical check-ups of other cohort profiles. It has only been about 10–15 years since the comprehensive health check-up programme was actively performed in Korea, and in the past decade, a large proportion of people participated in the check-up due to the support from the affiliated company's welfare policy. This might result in the relatively young population enrolment in our study population. But since the health check-up programme is getting more general, more elderly population is taking the health check-up. New enrolment is another future target study of our centre. Since the enrolled cohort population is relatively young, it is possible to study the preclinical disease stage and its final long-term outcomes. This might be the characteristics of our cohort that we could design a lot of prediction models for the NCD by using data from the preclinical stages. As we obtained a large sample size, we could confirm disease statuses as

well as numerous phenotypes of NCDs. Furthermore, the study protocols were conducted and monitored with intensive quality control procedures. Additional strengths include the active and passive follow-ups and the ability to obtain complete data, covering deaths and incidental cancer cases even among those who discontinued visiting our centre. We believe that these data could contribute to active, effective prevention against the development of cancers and NCDs.

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**Collaborators** The genotype (SNP) data from the GENIE study and the epidemiological data from the other cohorts are available to researchers after a quality control process has been completed. Potential collaborators can access the dataset after receiving approval from the SNUH Gangnam Center institutional review board. Applications can be submitted via our homepage. Further information is available at the H-PEACE study website (<http://en-healthcare.snuh.org/HPEACEstudy>).

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**Data sharing statement** Researchers can apply for the dataset after receiving approval from the SNUH Gangnam Center institutional review board. The H-PEACE study website provides information on the application process (<http://en-healthcare.snuh.org/HPEACEstudy>).

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