

## ORIGINAL ARTICLE

# Prevalence and correlates of orthostatic hypotension in middle-aged men and women in Korea: the Korean Health and Genome Study

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To examine the prevalence and correlates of orthostatic hypotension (OH) in middle-aged adults enrolled in the Korean Health and Genome Study. Participants were 8908 individuals aged 40–69 years. Supine blood pressure (BP) was measured three times at 30-s intervals after at least 5 min of rest in the supine position and single standing BP was measured at 0 and 2 min after standing, respectively. OH was defined as a reduction in systolic BP or diastolic BP  $\geq 20$  and 10 mmHg, respectively. The prevalence of OH at 0 and 2 min after standing was 12.3 and 2.9%, respectively. At 0 min of standing, OH frequency increased significantly with age from 6.4% in those aged 40–44 years to 23.1% in those aged 65–69 ( $P < 0.001$ ). After adjustment for age and other characteristics, hypertension was associated with a 1.7-fold excess in the odds of OH in men and a 1.6-fold excess in women ( $P < 0.001$ ). In contrast, an

increase in body mass index (BMI) on the order of 5 kg/m<sup>2</sup> was associated with a 20–30% reduction in the odds of OH ( $P < 0.001$ ). Diabetes in women was also associated with a 1.4-fold excess in the odds of OH ( $P < 0.05$ ). An increase in triglyceride by 136 mg/dl in men was associated with an increase in the odds of OH ( $P < 0.05$ ). In conclusion, the prevalence and correlates of OH other than diabetes and triglycerides were notably similar in men and women. While the association between hypertension and OH has been observed elsewhere, low BMI in Korean adults with OH may be an important marker for subclinical morbidity or coexisting risk factors that need to be identified.

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## Introduction

Orthostatic hypotension (OH) is a known risk factor for cardiovascular diseases and all-cause mortality.<sup>1–7</sup> Depending on how OH is measured, however, prevalence can range markedly from 5 to 30%,<sup>3–15</sup> making it difficult to describe cross-cultural variation or to identify effects that may be associated with OH.<sup>1,2,4,14,15</sup> Low rates of coronary heart disease in Asia vs the US and Western Europe suggest that the prevalence and correlates of OH may also be different through associations with risk factors that are culturally unique. Unfortunately, few studies of

OH have been conducted in Asia, and none have occurred in a general population setting in Korea. Limited data are also available in the middle aged. The purpose of this report is to examine the prevalence and correlates of OH in middle-aged men and women enrolled in the Korean Health and Genome Study.

## Materials and methods

### Background and study sample

The Korean Health and Genome Study began in 2001 as an ongoing population-based study of Korean adults aged 40–69 years. Support is from the Korean National Institute of Health for the purpose of describing the frequency and determinants of chronic diseases in Korea. Participants include residents of an industrialized community, 32 km southwest of Seoul, South Korea (Ansan) and in a rural setting, 100 km south of Seoul (Ansung).

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Procedures were in accordance with institutional guidelines and approved by an institutional review committee. Informed consent was obtained from the study participants.

Study enrolment was based on knowledge about community differences and on the most efficient method for recruiting representative samples of the Korean population. Since telephone use in Ansan is high, enrolment was based on random selection from directory listings that were made available on compact discs by local telephone companies. After 10 957 telephone calls, 2523 men and 2497 women agreed to participate in a baseline physical examination. In Ansong, sampling was based on mailing, door-to-door and telephone solicitations within five randomly selected governing regions (Myons) from a total of 11. After identifying 7192 eligible subjects, 2240 men and 2780 women underwent identical examinations as in Ansan. In both Ansan and Ansong, the age and sex distributions of those examined were similar to those who were not examined. Although, comparison of other characteristics is not possible, response rates are similar to other cohort studies.<sup>16–19</sup>

### Hypertension and orthostatic hypotension

Data on hypertensive status and OH were available in 9873 of the study participants. Among this group, those being treated for hypertension were excluded to eliminate the possibility of confounding due to blood pressure medication. The final sample included 8908 subjects.

Blood pressures (BPs) were measured with a mercury sphygmomanometer following a standardized protocol by a trained technician.<sup>20</sup> Measurement of sitting BP (with back support) was taken after a 5-min period of rest. At least two BP readings were recorded after a 30 s interval of time. If the first two readings differed by more than 5 mmHg, additional readings were obtained, and the average value was used as a measure of systolic (SBP) and diastolic BP (DBP). Hypertension was defined when either a SBP or DBP was  $\geq 140$  and 90 mmHg, respectively.<sup>20</sup>

Supine measurements were taken three times at 30-s intervals after at least 5 min of rest in the supine position. Average values were used as measures of supine systolic and DBPs. Standing measurements were taken at 0 and 2 min after standing. BPs measured at 0 min were taken at the moment after rising from the supine to standing positions (usually within 15 s from the last supine measurement). OH was defined as a drop in a SBP or DBP  $\geq 20$  and 10 mmHg, respectively.

### Other factors

Subjects received thorough questioning about demographic, dietary, and behavioural characteristics by

trained interviewers. Characteristics included age, sex, cigarette smoking status, body mass index (BMI), and measurements of lipids and fasting glucose. Current smoking was defined as smoking at least one cigarette per day for at least a year. After a 10-h fast, blood was drawn for determinations of total cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol. In addition to fasting glucose, glucose was also measured 2 h after a 75 g oral glucose challenge. The subjects were instructed not to drink alcohol for the 24-h period prior to their examinations, and to refrain from the intake of food after 2200 on the night before. Typical examinations began at 0900 the following morning. Total cholesterol and triglyceride levels were measured enzymatically by ADVIA 1650 (Bayer®, Germany), and HDL-cholesterol level was measured enzymatically with the same instrument after precipitation of the other lipoproteins. A diagnosis of diabetes was made if fasting levels were  $\geq 126$  mg/dl or when postchallenge levels were  $\geq 200$  mg/dl.<sup>21</sup> Diabetes was also defined when participants were receiving oral hypoglycaemic agents or insulin therapy.

### Statistical methods

Characteristics of the study sample are described separately for men and women and by the presence and absence of OH after adjustment for age based on standard analysis of covariance procedures and logistic regression models.<sup>22</sup> For hypertension, diabetes, and cigarette smoking, characteristics were modelled as dichotomous variables while the remaining factors, including age, were modelled as continuous variables. Coefficients for the latter variables also provided a test for trend in the changing prevalence of OH with changes in each of the continuous characteristics. For each characteristic, estimated regression coefficients and standard errors allowed for the calculation of the relative odds of OH (and 95% confidence intervals) according to selected risk factor differences. Here, the relative odds, after simultaneous adjustment for age and the other characteristics, provided a comparison of the odds of OH in subjects with and without hypertension, diabetes, and between smokers and nonsmokers. For continuous variables, the relative odds compare the odds of OH in persons at the 80th vs the 20th percentile of a characteristic. All reported *P*-values were based on two-sided levels of significance.

### Results

Among the 8908 study participants, 4328 were men and 4580 were women. Table 1 shows the age and age-adjusted characteristics of the study sample. Average age is similar in men and women (51.4 vs 51.7, respectively). Men were more likely to have hypertension and diabetes ( $P < 0.001$ ). Accordingly,

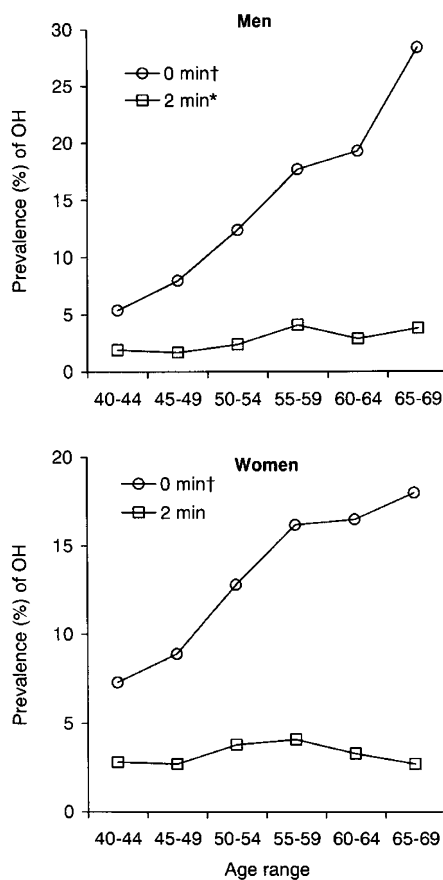
**Table 1** Age and age-adjusted characteristics in men and women enrolled in the Korean Health Study

Characteristic	Men (4328) <sup>a</sup>	Women (4580)
Age (years)	51.4 ± 8.7 <sup>b</sup>	51.7 ± 8.8
Hypertension (%)	25.1	19.3*
Diabetes (%)	12.5	9.6*
Cigarette smoker (%)	56.5	4.1*
SBP	120.8 ± 16.4	118.3 ± 18.1*
DBP	81.2 ± 10.7	77.6 ± 11.3*
BMI (kg/m <sup>2</sup> )	24.1 ± 4.1	24.7 ± 3.3*
Total cholesterol (mg/dl)	197.3 ± 37.2	197.7 ± 35.5
HDL cholesterol (mg/dl)	48.1 ± 12.2	51.5 ± 11.2*
Triglycerides (mg/dl)	168.0 ± 111.7	132.8 ± 105.2*

<sup>a</sup>Sample size.

<sup>b</sup>Mean ± s.d.

\*Significantly different from men ( $P < 0.001$ ).



Test for trend: \* $p < 0.05$ , † $p < 0.001$

**Figure 1** Prevalence (%) of OH at 0 and 2 min after standing by age and sex.

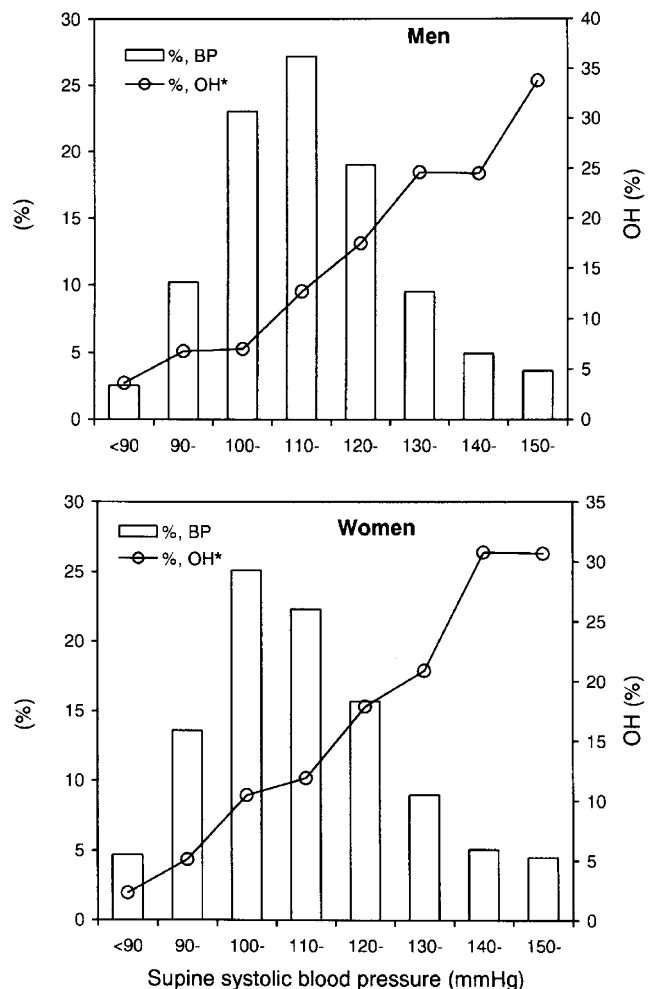
mean SBPs and DBPs were significantly higher in men vs women. Smoking in women was uncommon as compared to men (4.1 vs 56.5%, respectively,  $P < 0.001$ ). Although differences were modest, BMI was significantly less in men vs women. Men also had lower concentrations of HDL cholesterol than women (48.1 vs 51.5 mg/dl, respectively,  $P < 0.001$ ) and higher levels of triglycerides (168.0 vs 132.8 mg/dl, respectively,  $P < 0.001$ ). Total cholesterol levels were similar in men and women.

Overall, OH at either 0 or 2 min after standing was observed in 604 men (14.0%) and 630 women (13.8%). Figure 1 further describes the prevalence of OH according to age and sex.

The per cent of subjects with OH after 2 min of standing was uncommon in this middle-aged sample (2.5% in men and 3.1% in women). After 2 min of standing, there was a modest increase in the frequency of OH with increasing age in men (increasing from 1.9% in those aged 40–44 years to 3.8% in those aged 65–69 years,  $P < 0.05$ ), while OH at 2 min had no relation with age in women.

In contrast, at 0 min of standing, OH occurred frequently (12.6% in men and 11.9% in women). For both sexes, OH at 0 min of standing increased markedly with advancing age ( $P < 0.001$ ). For men, the frequency increased uniformly from 5.4% in those aged 40–44 years to 28.4% in those aged 65–69 years. Across the same age groups in women, the frequency increased from 7.3 to 18.0%.

The prevalence of OH was also positively associated with supine SBP levels in both men and women (see Figure 2). In men, 3.6% with a supine



\* Test for trend (p-value) < 0.001

**Figure 2** Prevalence (%) of OH at either 0 or 2 min after standing by sex and baseline supine SBP.

SBP <90 mmHg had OH at either 0 or 2 min after standing, while 33.8% had OH when BP was  $\geq 150$  mmHg. In women, a near identical pattern was observed. Similar findings occurred for supine DBP.

**Table 2** Age and age-adjusted characteristics in men and women with and without OH at either 0 or 2 min after standing

Characteristic	OH	
	Absent	Present
<i>Men</i>		
Number of subjects	3724	604
Age (years)	50.6 $\pm$ 8.5 <sup>a</sup>	56.0 $\pm$ 8.9**
Hypertension (%)	23.5	33.4**
Diabetes (%)	12.2	13.2
Cigarette smoker (%)	56.3	58.2
BMI (kg/m <sup>2</sup> )	24.1 $\pm$ 2.8	23.7 $\pm$ 2.9*
Total cholesterol (mg/dl)	197.2 $\pm$ 36.5	197.3 $\pm$ 37.1
HDL cholesterol (mg/dl)	47.9 $\pm$ 11.6	48.9 $\pm$ 11.8
Triglycerides (mg/dl)	166.5 $\pm$ 124.7	177.0 $\pm$ 126.7
<i>Women</i>		
Number of subjects	3950	630
Age (years)	51.3 $\pm$ 8.8	54.3 $\pm$ 8.8**
Hypertension (%)	18.4	25.4**
Diabetes (%)	9.2	12.1*
Cigarette smoker (%)	4.0	4.4
BMI (kg/m <sup>2</sup> )	24.1 $\pm$ 2.9	23.7 $\pm$ 2.9**
Total cholesterol (mg/dl)	197.1 $\pm$ 37.7	197.1 $\pm$ 37.8
HDL cholesterol (mg/dl)	48.0 $\pm$ 12.0	48.9 $\pm$ 12.1
Triglycerides (mg/dl)	166.1 $\pm$ 120.9	176.7 $\pm$ 129.2

<sup>a</sup>Mean  $\pm$  s.d.

\*Significantly different from those with OH ( $P < 0.01$ ).

\*\*Significantly different from those with OH ( $P < 0.001$ ).

Table 2 describes the age and age-adjusted characteristics in men and women with and without OH at either 0 or 2 min after standing. As might be expected, the presence of OH was associated with a more adverse cardiovascular risk profile. Regardless of sex, those with OH were older ( $P < 0.001$ ) and more likely to have hypertension ( $P < 0.001$ ) than those without OH. Diabetes was also more common in the presence of OH, although a significant excess was observed in only women ( $P < 0.01$ ). Despite higher prevalence of hypertension and diabetes, BMI is slightly but significantly lower in those with OH than in those without OH in both men ( $P < 0.01$ ) and women ( $P < 0.001$ ). Among the other characteristics, smoking was unrelated to OH, as were levels of total cholesterol, HDL-cholesterol, and triglyceride.

The estimated relative odds of OH at either 0 or 2 min after standing are shown in Table 3 based on a comparison between the presence vs the absence of hypertension and diabetes. Relative odds are also given for smokers as compared to nonsmokers and for subjects at the 80th vs the 20th percentile of a continuous characteristic. When OH is defined separately at 0 and 2 min after standing, associations are similar to those described in Table 3.

As seen in Table 3, associations between a study characteristic and OH were comparable in men and women. In men, however, an increase in triglycerides by 136 mg/dl was associated with a slight but significant increase in the odds of OH ( $P < 0.05$ ), while in women, diabetes was associated with 1.4-fold excess in the odds of OH ( $P < 0.05$ ). After adjustment for age and the other characteristics, hypertension was associated with a 1.7-fold excess

**Table 3** Estimated relative odds of OH at either 0 or 2 min after standing in men and women due to characteristic comparisons

		Relative odds	
Characteristic	Comparison groups	Adjusted for age	Adjusted for age and the other characteristics
Men			
Hypertension	Present vs absence	1.7*** (1.4, 2.0)	1.7*** (1.4, 2.1)
Diabetes	Present vs absence	1.1 (0.9, 1.4)	1.1 (0.8, 1.4)
Cigarette smoker	Yes vs no	1.1 (0.9, 1.3)	1.0 (0.8, 1.2)
BMI	4.8 kg/m <sup>2a</sup>	0.8** (0.7, 0.9)	0.7*** (0.6, 0.9)
Total cholesterol	60 mg/dl <sup>a</sup>	1.0 (0.9, 1.2)	1.0 (0.8, 1.1)
HDL cholesterol	18 mg/dl <sup>a</sup>	1.1 (1.0, 1.3)	1.1 (0.9, 1.2)
Triglycerides	136 mg/dl <sup>a</sup>	1.1** (1.0, 1.2)	1.1* (1.0, 1.2)
Women			
Hypertension	Present vs absence	1.6*** (1.3, 1.9)	1.6*** (1.3, 2.0)
Diabetes	Present vs absence	1.4* (1.1, 1.8)	1.4* (1.0, 1.8)
Cigarette smoker	Yes vs no	1.1 (0.7, 1.6)	1.0 (0.7, 1.6)
BMI	5.1 kg/m <sup>2a</sup>	0.9** (0.8, 1.0)	0.8* (0.7, 1.0)
Total cholesterol	59 mg/dl <sup>a</sup>	1.0 (0.9, 1.2)	1.1 (0.9, 1.3)
HDL cholesterol	19 mg/dl <sup>a</sup>	1.0 (0.9, 1.1)	1.0 (0.8, 1.1)
Triglycerides	100 mg/dl <sup>a</sup>	1.0 (1.0, 1.1)	1.0 (0.9, 1.1)

<sup>a</sup>Comparison is based on the difference between the characteristic at the 80th minus the 20th percentiles.

Significant odds ratio: \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ .

in the odds of OH in men and a 1.6-fold excess in women ( $P < 0.001$ ). In contrast, an increase in BMI on the order of  $5 \text{ kg/m}^2$  was associated with a 30% reduction in the odds of OH in men ( $P < 0.01$ ), and a 20% reduction in women ( $P < 0.001$ ). After adjustment for age and the other characteristics, cigarette smoking and levels of total cholesterol and HDL cholesterol had no apparent association with OH in either sex.

## Discussion

The overall prevalence of OH at 0 or 2 min after standing in the middle-aged population-based sample in the Korean Health and Genome Study was 13.8% (1234/8908). Prevalence and correlates of OH (age, hypertension, and BMI) were also notably similar in men and women.

After 2 min of standing, OH was uncommon (2.9%) relative to other population-based samples. In the Atherosclerosis Risk in Communities (ARIC) study, which is a survey of Caucasian and Black men and women aged 45–64 years, prevalence was 5%.<sup>1,2</sup> This difference in the prevalence of OH between studies is largely due to methodological differences. As noted in our methods, we measured supine BP three times after at least 5-min of rest and a single standing BP at 0 and 2 min of standing. In the ARIC study, however, supine BPs were taken for 2 min with an automated oscillometric device after a 20 min supine rest, and in the same manner, standing BPs were taken after subject's feet touched the ground.<sup>1,2</sup> As discussed by the authors of the ARIC study, the use of average standing BPs, rather than a single standing BP, seemed to avoid missing OH if a single standing BP is used since measuring standing pressure at 1 vs 3 min may identify different individuals.<sup>2</sup> Therefore, the prevalence of OH in the ARIC study is higher than the prevalence of OH at 2 min of standing in the current study.

While some differences are due in part to how OH is defined, differences in the frequency of OH could also be attributed to dietary, behavioural, physical, and genetic factors that are unique to Asian and Western cultures. The lower rate of OH after 2 min of standing may also mirror the low rates of coronary heart disease that are consistently observed in developed regions of Asia.

Differences in the prevalence of OH between other ethnic groups are less clear. In the Systolic Hypertension in the Elderly Project (SHEP)<sup>13</sup> and the Cardiovascular Health Study,<sup>4</sup> no significant differences were observed in the prevalence of OH between ethnic groups, mainly composed of Caucasian and Black individuals. In a survey in two rural communities, however, prevalence of OH was twice as common in elderly Caucasians as compared to Blacks,<sup>14</sup> while in the ARIC study,<sup>1,2</sup> systolic OH was observed to be higher in Blacks than in Caucasians.

Most studies of OH have focused on the elderly,<sup>3–6,8–15</sup> where reported prevalence ranges from 5 to 30%. Unfortunately, the use of different methods to define OH makes it difficult to compare study findings.<sup>23</sup> Recently, the American Autonomic Society and the American Academy of Neurology have defined OH as a reduction in SBP or DSP by  $\geq 20$  and 10 mmHg, respectively, within 3 min of standing.<sup>24,25</sup> Whether different timing of measurements is better suited for men than women according to age warrants consideration. In the Korean Health and Genome Study, OH was uncommon at 2 min after standing, and presumably it would have been less after 3 min. Whether subjects with OH at 0 min are more likely to progress to OH, that lasts for a longer period of time is also worth considering.

Consistent with earlier reports,<sup>1,2,4,6,7</sup> the prevalence of OH in this population-based sample increased with age, but the increase was less clear for OH measured after 2 min of standing. An association between age and the latter measure of OH was absent in women. It is well known, however, that normal ageing is associated with diminished cardiovascular compliance and distensibility with effects on cardiac output at supine rest and postural hypotension.<sup>26</sup> Ageing is also related to elevations in SBP, poor tolerance to volume reduction, and autonomic insufficiency, all of which can contribute to OH.

Even in instances where the prevalence of OH is similar between groups, wide variation in characteristics, especially age and comorbidity, and the definition of OH, continues to make it difficult to make comparisons.<sup>4,5,8,9,13</sup> In the ARIC study, those with OH were more likely to smoke cigarettes,<sup>1,2</sup> whereas others found no significant relation with smoking.<sup>4,13</sup> In the Korean Health and Genome Study, OH was also unrelated to smoking. If smoking were a factor in Korea, one might have expected a much higher prevalence of OH in men than in women.

An association between BMI and OH is equally unclear.<sup>1–3,5,6,10,11,13,14</sup> In the current report, lower BMI was positively related to an excess in the odds of OH. Although findings were adjusted for age, hypertension, diabetes, cigarette smoking, total cholesterol, HDL cholesterol, and triglycerides, other unknown comorbidities in leaner individuals are likely to have contributed to this finding. These data suggest that OH in lean individuals may also be an important marker for other conditions that need to be identified. Factors, such as heart rate, electrocardiographic abnormality, and peripheral vascular disease, also need consideration. Dietary factors, such as sodium intake, were not related to OH in our study.

In contrast to hypertension, BMI, diabetes in women and triglyceride in men, total cholesterol, and HDL cholesterol had weak or inconsistent associations with OH in the Korean sample. In the Helsinki Aging Study, OH was also unrelated to total

cholesterol and triglycerides, although HDL cholesterol was lower in the subjects with symptomatic OH than in those without OH.<sup>10</sup> In the ARIC study, HDL cholesterol was also lower in the presence of OH and low-density lipoprotein cholesterol was higher.<sup>1,2</sup>

Unfortunately, population-based data are not available for making similar comparisons throughout much of Asia. This is the first large-scale study of the prevalence and correlates of OH in a middle-aged population-based sample in Korea. The Korean Health and Genome Study is also an initial entry by the Korean government into large-scale epidemiologic research. While it represents a major investment in describing the distribution and determinants of chronic diseases in Korea, the study also faces the usual limitations that exist elsewhere.<sup>16–19</sup> Although study participants will receive subsequent examinations, only the first cycle is complete, and OH incidence cannot be examined at the present time. Findings are also limited to those who are ambulatory. The possible bias from responders being healthier than nonresponders, common in any large-scale epidemiologic study, can also not be fully assessed. Nevertheless, the study sample includes a broad range of physiologic and clinically important risk factors, including BP, serum glucose, smoking histories, BMI, and lipid profiles. As a result, findings are likely to be relevant for most Koreans and provide a useful resource for cross-cultural comparisons.

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