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ORIGINAL RESEARCH

Very High Prevalence of Nonoptimally Controlled Traditional Risk Factors at the Onset of Cardiovascular Disease

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ABSTRACT

BACKGROUND Recent studies suggest that coronary heart disease (CHD) may frequently occur in the absence of traditional cardiovascular disease (CVD) risk factors. However, it is unclear whether this could reflect missed clinical diagnoses or subthreshold nonoptimal risk factor exposure preceding CHD, and whether similar patterns are observed for heart failure (HF) or stroke.

OBJECTIVES The purpose of this study was to determine the antecedent occurrence of nonoptimal levels of 4 traditional risk factors (blood pressure [BP], cholesterol, glucose, and tobacco smoking) before first CHD, HF, or stroke.

METHODS We analyzed 2 population-based prospective cohorts: KNHIS (Korean National Health Insurance Service) (n = 9,341,100; baseline age ≥20 years; follow-up, 2009-2022) and MESA (Multi-Ethnic Study of Atherosclerosis) (n = 6,803; baseline age 45-84 years; follow-up, 2000-2019). Among individuals who developed incident CHD, HF, or stroke during follow-up, we determined the prevalence of ≥1 traditional risk factor above optimal level—systolic BP ≥120 mm Hg or diastolic BP ≥80 mm Hg or BP-lowering treatment; total cholesterol ≥200 mg/dL or lipid-lowering treatment; fasting glucose ≥100 mg/dL or diagnosis of diabetes or glucose-lowering treatment; or past or current smoking—at any visit before CVD.

RESULTS Analyses were based on 601,025 and 1,188 CVD events in KNHIS and MESA, respectively. Prevalence of ≥1 nonoptimal risk factor was high (99.7% and 99.6%) before CHD, with similar patterns before HF (99.4% and 99.5%) and stroke (99.3% and 99.5%) in both KNHIS and MESA, respectively. Prevalence of ≥1 risk factor before CVD was consistently high (>99%) across age groups in both men and women, with the lowest proportion observed for HF and stroke (>95%) when occurring at ages <60 years in women. Prevalence of ≥2 risk factors was also common (93.2% to 97.2%) before CVD events.

CONCLUSIONS In this binational study of 2 prospective cohorts, the presence of nonoptimal levels of ≥1 traditional risk factor was nearly universal before CVD. These results not only challenge claims that CHD events frequently occur without antecedent major risk factors but also demonstrate that other CVD events, including HF or stroke, rarely occur in the absence of nonoptimal traditional risk factors, highlighting the importance of primordial prevention efforts. (JACC. 2025;86:1017–1029) © 2025 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CHD = coronary heart disease

CVD = cardiovascular disease

CVH = cardiovascular health

HF = heart failure

MI = myocardial infarction

SMuRF = standard modifiable cardiovascular risk factor

Traditional cardiovascular disease (CVD) risk factors, including hypertension, hypercholesterolemia, diabetes, and tobacco use, have been a major focus of research as well as clinical and public health prevention practice for decades.[1] However, national data sets highlight that awareness is low and diagnosis of risk factors is frequently missed in clinical practice.[2] Moreover, large cohort studies have shown that optimal (ie, very low risk) levels of CVD risk factors are lower than those used to define treatment thresholds in clinical practice guidelines.[3-6] The importance of nonoptimal levels of CVD risk factors and their contribution to population burden of CVD have intensified over the past decade with efforts such as the development of the novel American Heart Association (AHA) cardiovascular health (CVH) construct.[1] Initially defined as Life's Simple 7 and recently updated as Life's Essential 8,[7] this positive health-based (rather than risk- or disease-based) framing focuses on achieving and maintaining optimal levels of health factors to improve population health. However, there is a low prevalence of optimal traditional risk factor levels in most general populations.[8-10]

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Despite a well-established evidence base on the importance of antecedent traditional risk factors preceding CVD events,[11,12] recent studies have reported that the proportion of coronary heart disease (CHD) patients presenting without any traditional CVD risk factors is substantial and actually increasing.[13-15] A recent review[13] and meta-analysis[14] reported that more than 11% and up to 27% of patients presenting with acute coronary syndromes lacked evidence of any of the 4 standard modifiable CVD risk factors (SMuRFs). However, in most of the studies these authors cited, presence or absence of antecedent risk factors was based on prior *clinical* diagnosis of hypertension, hypercholesterolemia, diabetes, and current smoking, which requires clinical contact, appropriate screening, and awareness of diagnostic thresholds, and thus could create significant misclassification. In addition, as the burden of other CVD subtypes, including heart failure (HF) and stroke, continues to rise, understanding the antecedent prevalence of traditional CVD risk factors before any CVD event is critical to inform prevention strategies.

To address these questions, we leveraged data from 2 prospective cohort studies of binational, diverse, contemporary population-based samples, in which repeated risk factor levels were assessed longitudinally. Among the subsets who experienced CVD events, we determined the prevalence of any antecedent exposure to major nonoptimal risk factors before the development of first CHD, HF, or stroke event.

METHODS

The 2 cohorts were the KNHIS (Korean National Health Insurance Service) and the MESA (Multi-Ethnic Study of Atherosclerosis). These cohorts included data on CVD events and repeated measurements of antecedent risk factor levels with extensive and complete follow-up.

KNHIS DATABASE. The KNHIS is the single provider of universal health insurance in South Korea. The KNHIS database contains deidentified information on sociodemographics, health insurance reimbursement claims, and vital status of the entire South Korean population.[16] The database also incorporates the results of routine biennial health examinations provided by the KNHIS to all Korean adults.[17] During each KNHIS health examination, tobacco smoking status was self-reported as never, past, or current smoking; blood pressure (BP) was measured by trained health care personnel using auscultatory or oscillometric methods in seated participants; and fasting glucose, total cholesterol, and high-density lipoprotein (HDL) cholesterol were measured by each health screening institution as overseen by the KNHIS and the Korean Association of Laboratory Quality Control.[17] The use of BP-, glucose-, and lipid-lowering drugs were determined from insurance claims data during a 2-year look-back period from each health examination. Additional details of the KNHIS database and health examination have been previously reported.[16,17]

Of 10,449,327 Korean adults aged 20 years or older who participated in the 2009 KNHIS health examination, which served as the baseline for this cohort, those with no data on ≥1 risk factor at baseline (n = 515,234), and those with a prior history of CHD, HF, or stroke (n = 592,993) were excluded (Supplemental Figure 1). The complete baseline set was taken for comparability with the near-complete MESA baseline and to guarantee that all participants had at least 1 nonmissing value for each risk factor's presence or absence to be determined before an outcome event. In the remaining 9,341,100 participants, CVD events were ascertained by the International Classification of Diseases-10th Revision (ICD-10) codes[18-21] from hospitalization claims data and linkage to the Statistics Korea death registry with documented causes of death (Supplemental Table 1) during follow-up through December 31, 2022. The

study protocol was approved by the Institutional Review Board of Severance Hospital, Seoul, Korea (Y-2021-0135; 4-2023-0165). Written informed consent was waived, because the study was based on anonymized administrative data.

MULTI-ETHNIC STUDY OF ATHEROSCLEROSIS. The MESA, launched in July 2000, examines the prevalence, correlations, and progression of subclinical CVD in 6,814 adults aged 45 to 84 years.[22] Participants with no clinical CVD history were recruited from 6 U.S. centers. Approximately 38% of the participants self-identified as non-Hispanic White, 28% as non-Hispanic Black, 23% as Hispanic, and 11% as Chinese American individuals. Blood samples were analyzed for traditional risk factors, including fasting cholesterol and glucose. Key risk factors were reassessed repeatedly in-person, with follow-up through 2019 for CVD events and mortality.

Of 6,814 U.S. adults enrolled in MESA at baseline, participants with no data at any visit on ≥1 risk factor (n = 11) were excluded (Supplemental Figure 1). In the remaining 6,803 participants, CVD events in MESA were captured through active surveillance via regular participant contact, systematic retrieval of medical records, and centralized adjudication by physician expert committees using standardized definitions. The study protocol was approved by the Institutional Review Boards of the participating institutions, and all participants provided written informed consent at time of enrollment.

OUTCOME DEFINITIONS. Five outcome events were studied separately: CHD, myocardial infarction (MI), HF, stroke, and total CVD events. A CHD event was defined as incident MI or death caused by CHD. A total CVD event was defined as incident MI, HF, stroke, or death caused by CVD. The first occurrence of each outcome was considered an incident event.

RISK FACTOR DEFINITIONS. Exposure to risk factors was determined using all available repeated measurements at baseline and throughout follow-up before a CVD event. Definitions of nonoptimal risk factors were based on AHA's ideal CVH framework, reflecting evidence that optimal levels of risk factors are lower than commonly recognized and treated in clinical practice.[1] Accordingly, nonoptimal risk factors were defined as systolic BP ≥120 mm Hg or diastolic BP ≥80 mm Hg or BP-lowering treatment; total cholesterol ≥200 mg/dL (≥5.17 mmol/L) or lipid-lowering treatment; fasting glucose ≥100 mg/dL (≥5.55 mmol/L) or diagnosis of diabetes or glucose-lowering treatment; or past or current tobacco smoking at any point among all available examination visits before the outcome event (Supplemental Table 2).[23] As a secondary analysis, exposure to a clinically elevated risk factor was defined with higher cut points as often used for clinical diagnosis: systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg or BP-lowering treatment; total cholesterol ≥240 mg/dL (≥6.21 mmol/L) or lipid-lowering treatment; or fasting glucose ≥126 mg/dL (≥6.99 mmol/L) or diagnosis of diabetes or glucose-lowering treatment at any point among all available examination visits before the outcome event; or current tobacco smoking at the last examination before the outcome event (Supplemental Table 2).

STATISTICAL ANALYSES. Analyses were conducted separately by cohort and by event type. Demographics of the participants were reported as mean ± SD or number (%) as appropriate. The proportion of participants exposed to a nonoptimal risk factor was calculated as the number who had the antecedent risk factor divided by the number who had the event. The 95% CI of a proportion was calculated by the normal approximation to the binomial distribution, except where the proportion was 100%, in which case the lower bound was calculated by the Clopper-Pearson exact method. The analyses were further stratified by sex and event age (<60, 60-69, 70-79, and ≥80 years). Analyses were performed using SAS version 9.4 (SAS Institute Inc) or R version 4.0.3 (R Foundation for Statistical Computing).

SENSITIVITY ANALYSES. The following sensitivity analyses were conducted. First, non-HDL cholesterol ≥130 mg/dL (≥3.36 mmol/L), ≥100 mg/dL (≥2.59 mmol/L), or low-density lipoprotein (LDL) cholesterol ≥70 mg/dL (≥1.81 mmol/L) was used in place of total cholesterol ≥200 mg/dL as the nonoptimal lipid level, given that total cholesterol 200 mg/dL may not be a sufficiently stringent cut point, and that some individuals with low total cholesterol may have undesirable levels of HDL and non-HDL cholesterol.[7] Second, for the analysis of each CVD subtype, participants who experienced another CVD subtype before the outcome of interest were excluded (ie, only the first subtype of CVD event was analyzed), ensuring that exposure to risk factors was not influenced by the occurrence of another CVD subtype. Third, deaths from CHD and from CVD (fatal components of CHD and total CVD events, respectively) were analyzed separately to explore whether results were consistent for fatal CVD events. Fourth, instead of the complete baseline set used in KNHIS for comparability with the near-complete MESA baseline, a less exclusive KNHIS sample was taken by removing only participants with no data at any visit on ≥1 risk factor.

TABLE 1 Demographics of the KNHIS and MESA Participants With Incident CVD Events

	Incident CVD Event				
	CHD	MI	HF	Stroke	Total CVD
KNHIS					
n	96,097	76,558	294,220	259,348	601,025
Age, y					
First examination	58.6 ± 12.9	57.0 ± 12.4	61.5 ± 12.7	60.5 ± 12.4	60.5 ± 12.8
Event	66.1 ± 12.9	64.6 ± 12.3	70.5 ± 12.6	67.8 ± 12.4	68.5 ± 12.8
Sex					
Female	23,150 (24.1)	16,838 (22.0)	133,568 (45.4)	105,572 (40.7)	244,134 (40.6)
Male	72,947 (75.9)	59,720 (78.0)	160,652 (54.6)	153,776 (59.3)	356,891 (59.4)
MESA					
n	537	374	433	377	1,188
Age, y					
First examination	67.0 ± 10.1	65.7 ± 10.2	67.9 ± 8.9	67.1 ± 9.5	67.2 ± 9.6
Event	75.9 ± 10.5	74.5 ± 10.6	76.9 ± 9.8	76.5 ± 9.9	76.1 ± 10.2
Sex					
Female	212 (39.5)	147 (39.3)	188 (43.4)	191 (50.7)	521 (43.9)
Male	325 (60.5)	227 (60.7)	245 (56.6)	186 (49.3)	667 (56.1)
Race/ethnicity					
White	211 (39.3)	164 (43.9)	179 (41.3)	141 (37.4)	464 (39.1)
Black	143 (26.6)	81 (21.7)	136 (31.4)	109 (28.9)	349 (29.4)
Hispanic/Latino	131 (24.4)	95 (25.4)	88 (20.3)	97 (25.7)	269 (22.6)
Chinese	52 (9.7)	34 (9.1)	30 (6.9)	30 (8.0)	106 (8.9)

Values are n, mean ± SD, or n (%).

CHD = coronary heart disease; CVD = cardiovascular disease; HF = heart failure; KNHIS = Korean National Health Insurance Service; MESA = Multi-Ethnic Study of Atherosclerosis; MI = myocardial infarction.

RESULTS

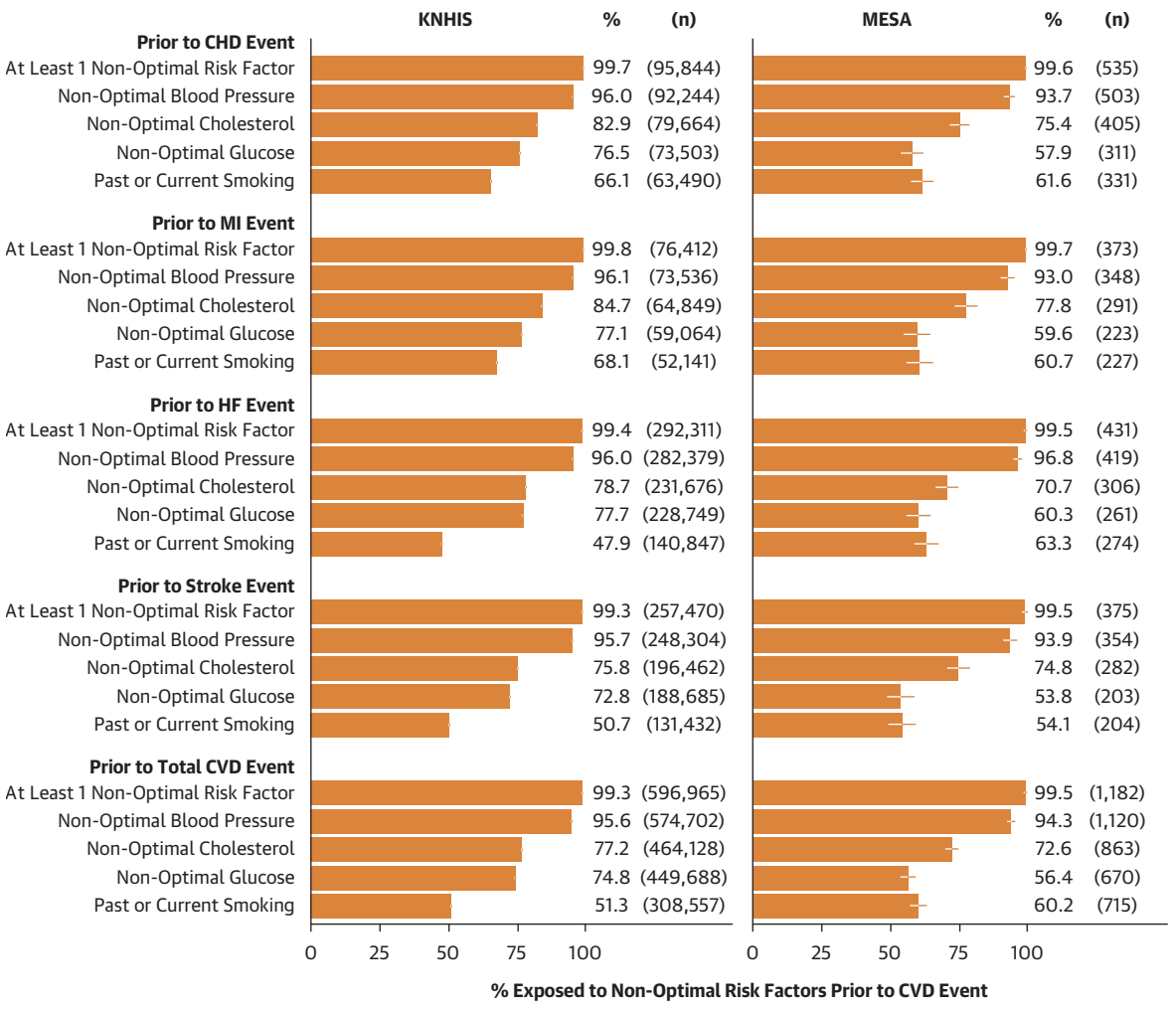
Analyses of the KNHIS cohort were conducted on 96,097 CHD events, 76,558 MI events, 294,220 HF events, 259,348 stroke events, and 601,025 total CVD events, which occurred over a median follow-up period of 13.3 years after the first examination. Analyses of the MESA cohort were conducted on 537 CHD events, 374 MI events, 433 HF events, 377 stroke events, and 1,188 total CVD events, which occurred over a median follow-up period of 17.7 years after the first examination. Table 1 shows the demographics of the KNHIS and MESA participants by outcome events. The mean age at CVD events ranged from 64.6 to 70.5 years in KNHIS and from 74.5 to 76.9 years in MESA. The proportion of female sex ranged from 22.0% to 45.4% in KNHIS and from 39.3% to 50.7% in MESA, depending on the CVD subtype. The distribution of race/ethnicity in MESA is provided in Table 1. In both cohorts, the median number of visits per participant for risk factor measurement was 4, before a CVD event.

EXPOSURE TO AT LEAST 1 NONOPTIMAL RISK FACTOR BEFORE CVD EVENTS. For all CVD event subtypes, the proportion of participants exposed to antecedent nonoptimal risk factors exceeded 99% (Figure 1). In KNHIS and MESA, respectively, the proportions exposed to at least 1 nonoptimal risk factor were 99.7% and 99.6% before CHD events; 99.8% and 99.7% before MI events; 99.4% and 99.5% before HF events; 99.3% and 99.5% before stroke events; and 99.3% and 99.5% before total CVD events.

When considered by individual risk factor, antecedent exposure to nonoptimal BP ranged from 95.6% to 96.1% in KNHIS and 93.0% to 96.8% in MESA; nonoptimal cholesterol, 75.8% to 84.7% in KNHIS and 70.7% to 77.8% in MESA; nonoptimal glucose, 72.8% to 77.7% in KNHIS and 53.8% to 60.3% in MESA; and past or current smoking, 47.9% to 68.1% in KNHIS and 54.1% to 63.3% in MESA (Figure 1). Exposure to 2 or more nonoptimal risk factors was also very common: 93.4% to 97.2% in KNHIS and 93.2% to 94.9% in MESA (Figure 2, Supplemental Figure 2).

In both cohorts, the proportion of men and women exposed to at least 1 nonoptimal risk factor before CVD events was further stratified by age at the time of event (Figures 3 and 4). In KNHIS, the proportions among men were remarkably similar, exceeding 99% across all age groups and CVD event subtypes. The

FIGURE 1 Exposure to Nonoptimal Risk Factors Before CVD Events



Data are presented as the number and % exposed to nonoptimal risk factors among the total number of events for each outcome. Horizontal error bars represent 95% CIs. For KNHIS (Korean National Health Insurance Service), error bars may be too narrow to be visible. Exposure to a nonoptimal risk factor was defined as systolic blood pressure (BP) ≥120 mm Hg or diastolic BP ≥80 mm Hg or BP-lowering treatment; total cholesterol ≥200 mg/dL or lipid-lowering treatment; fasting glucose ≥100 mg/dL or diagnosis of diabetes or glucose-lowering treatment; or past or current tobacco smoking at any point among all available examination visits before the outcome event. CHD = coronary heart disease; CVD = cardiovascular disease; HF = heart failure; MESA = Multi-Ethnic Study of Atherosclerosis; MI = myocardial infarction.

proportions among women also remained consistently high: >99% at age ≥60 years and >95% at age <60 years at event. In MESA, nearly all men and women across all age groups were exposed to at least 1 nonoptimal risk factors.

EXPOSURE TO AT LEAST 1 CLINICALLY ELEVATED RISK FACTOR BEFORE CVD EVENTS. Exposure to antecedent risk factors was still the rule (90%-95%) when higher cut points were used to define clinically elevated levels of the continuous risk factors (**Figure 5**). Clinically elevated BP was again the most common antecedent risk factor exposure. Predictably, the majority of participants without clinically-elevated risk factors still had at least 1 nonoptimal risk factor before CVD events. Most exhibited multiple nonoptimal, if not clinically-elevated, risk factors, with 97% to 99% being exposed to ≥1 clinically-elevated or ≥2 nonoptimal risk factors (Supplemental Figure 3).

SENSITIVITY ANALYSIS. First, when non-HDL cholesterol ≥130 mg/dL was used instead of elevated total cholesterol as 1 of the nonoptimal risk factors,

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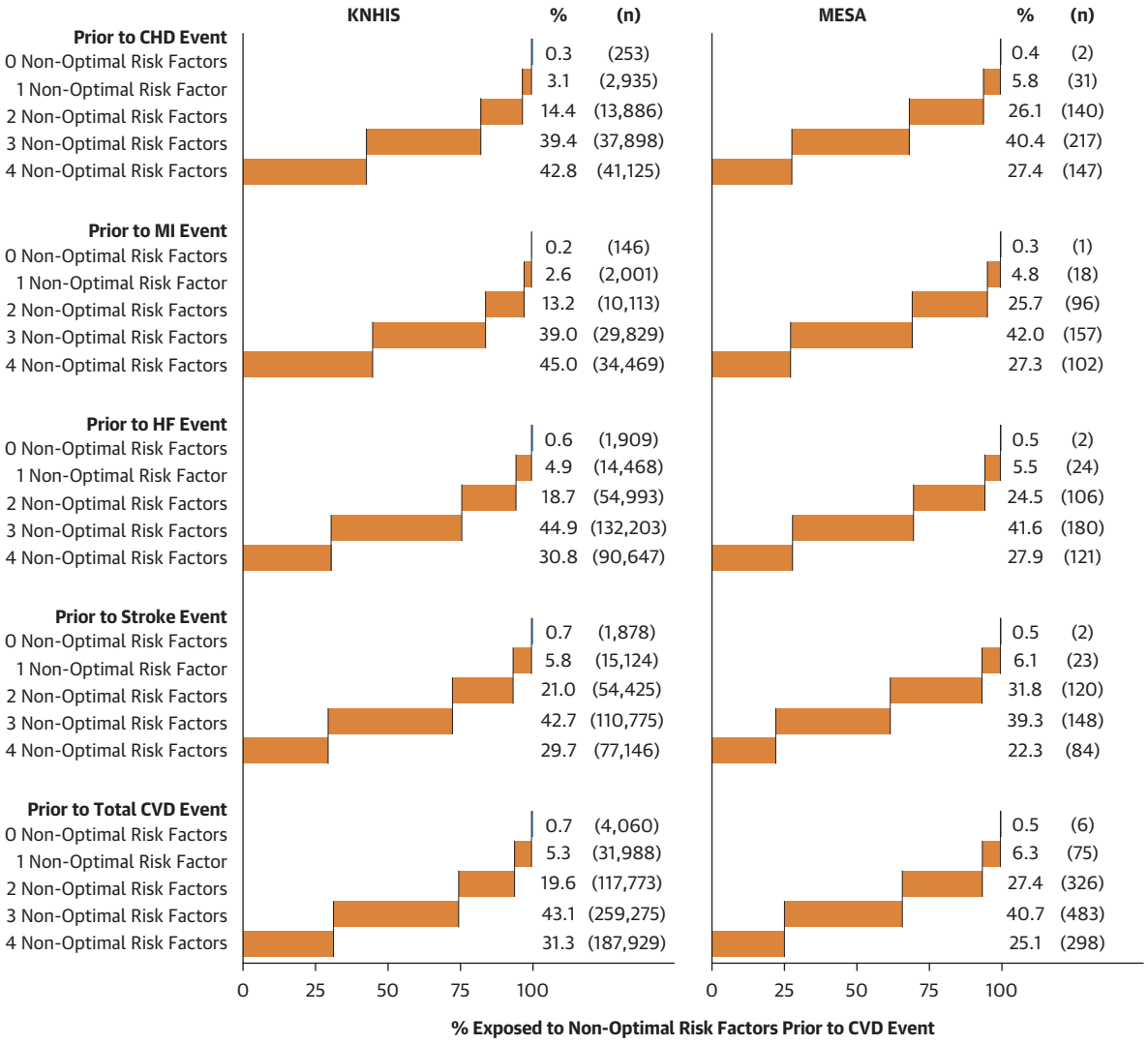
FIGURE 2 Number of Nonoptimal Risk Factors Present Before CVD Events

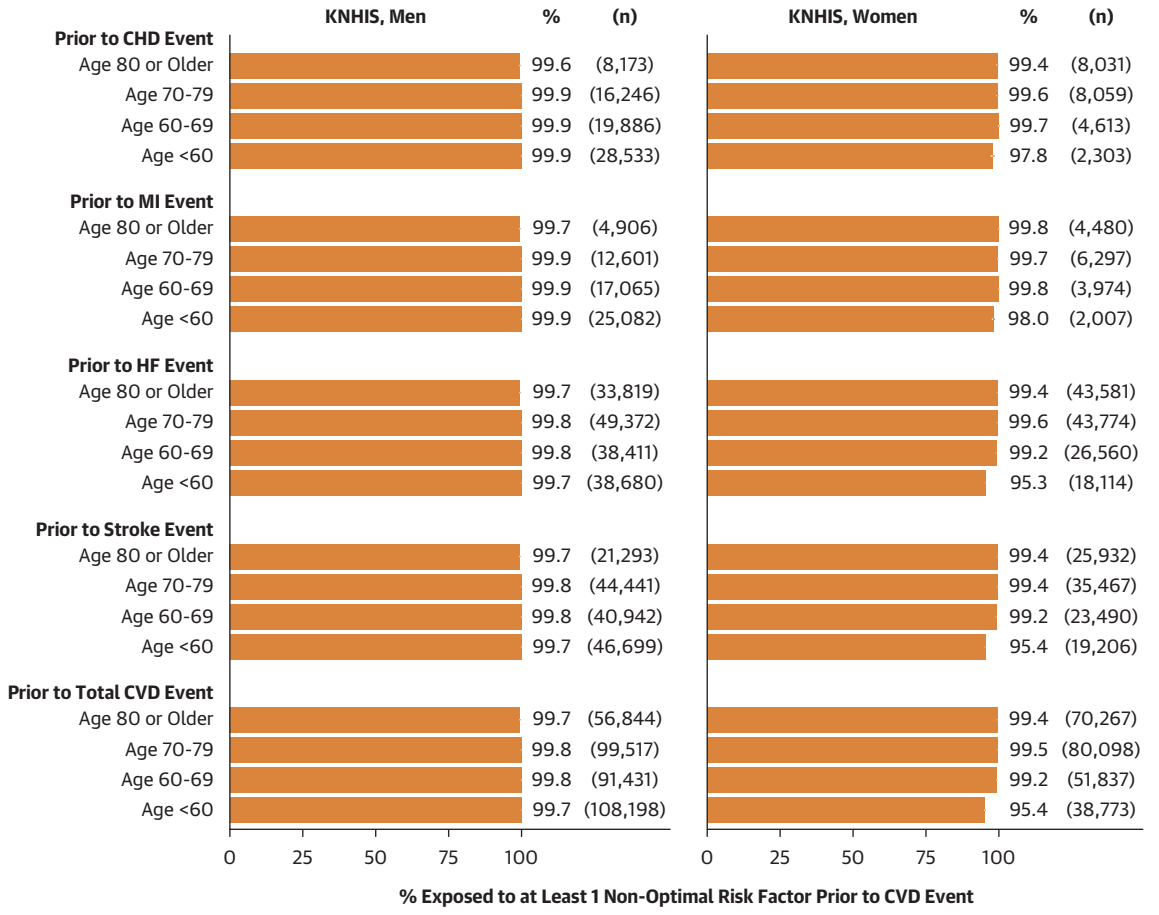


Each bar width represents % exposed to the given number of nonoptimal risk factors among the total number of events for each outcome. Bars representing 0 risk factors (blue) may be too narrow to be visible. Exposure to a nonoptimal risk factor was defined as systolic BP ≥120 mm Hg or diastolic BP ≥80 mm Hg or BP-lowering treatment; total cholesterol ≥200 mg/dL or lipid-lowering treatment; fasting glucose ≥100 mg/dL or diagnosis of diabetes or glucose-lowering treatment; or past or current tobacco smoking at any point among all available examination visits before the outcome event. Abbreviations as in **Figure 1**.

the prevalence of at least 1 antecedent nonoptimal risk factor was even higher, ranging from 99.5% to 99.9% (Supplemental Figure 4). With lower lipid cut points (non-HDL cholesterol ≥100 mg/dL or LDL cholesterol ≥70 mg/dL), the prevalence reached 100% (Supplemental Figures 5 and 6). Second, when only the first subtype of CVD event was analyzed as the outcome of interest, prior exposure to at least 1 nonoptimal risk factors was similarly universal (Supplemental Figure 7). Third, the results were consistent for death from CHD and from CVD analyzed as separate CVD subtypes (Supplemental Figure 8). Fourth, the results were identical in a less exclusive KNHIS sample removing only participants with no data on one or more risk factors at any visit during follow-up (Supplemental Figure 9).

POST HOC ANALYSIS OF INDIVIDUALS WITHOUT CVD EVENTS. There were 8,740,075 individuals in KNHIS and 5,615 individuals in MESA who did not

FIGURE 3 Exposure to at Least 1 Nonoptimal Risk Factor Before CVD Events in KNHIS by Sex and Age at the Time of Event



Data are presented as the number and % exposed to nonoptimal risk factors among the total number of events for each outcome and stratum. Horizontal error bars, representing 95% CIs, may be too narrow to be visible. Exposure to a nonoptimal risk factor was defined as systolic BP ≥120 mm Hg or diastolic BP ≥80 mm Hg or BP-lowering treatment; total cholesterol ≥200 mg/dL or lipid-lowering treatment; fasting glucose ≥100 mg/dL or diagnosis of diabetes or glucose-lowering treatment; or past or current tobacco smoking at any point among all available examination visits before the outcome event. Abbreviations as in Figure 1.

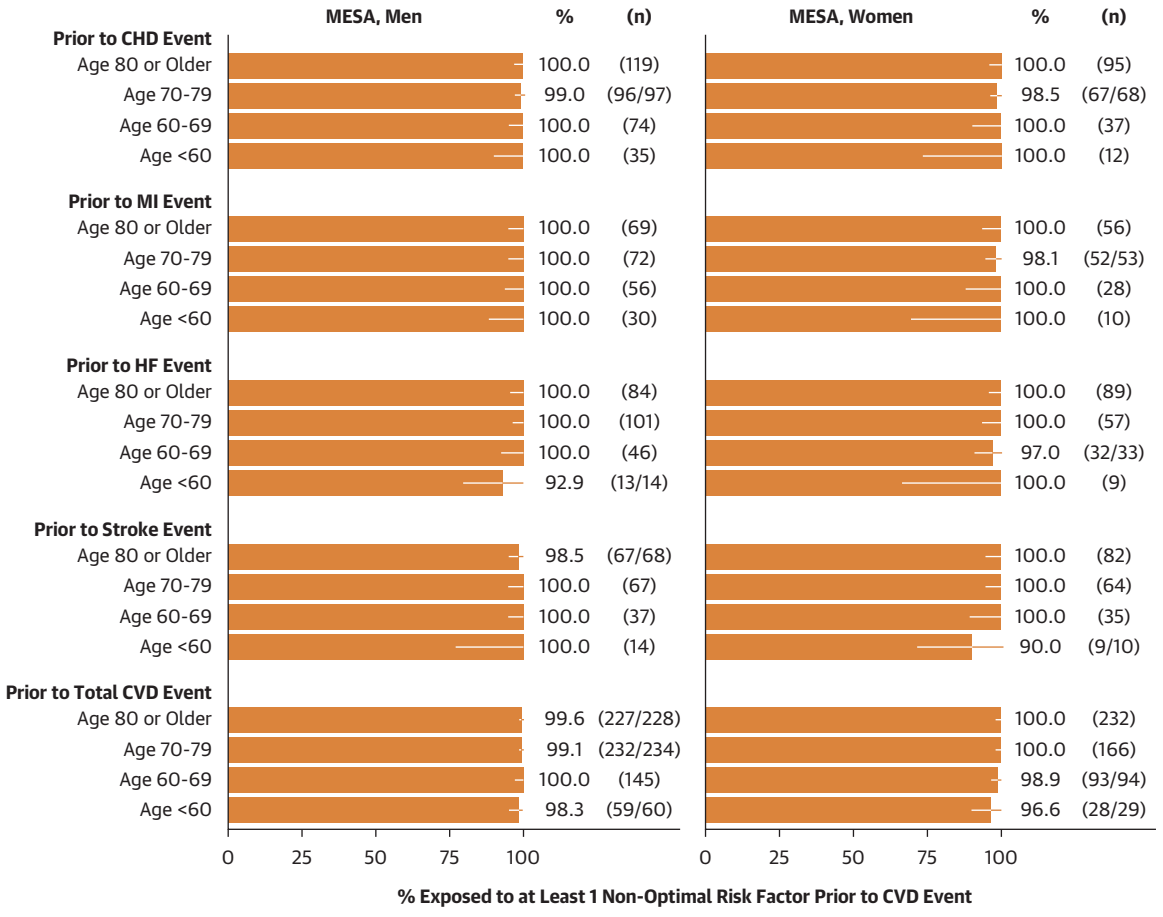
experience CVD events during the follow-up period. Among them, exposure to at least 1 nonoptimal risk factor were 98.4% and 97.6%, and exposure to at least 1 clinically elevated risk factor were 78.6% and 84.0% in KNHIS and MESA, respectively (Supplemental Figure 10).

DISCUSSION

This binational population-based cohort study demonstrated that nearly all individuals (>99%) had at least 1 nonoptimal traditional risk factor before their first CVD event (**Central Illustration**). This was similarly observed across CVD subtypes with nearly universal antecedent exposure to nonoptimal traditional risk factors before CHD, MI, HF, or stroke. Findings were also consistent by sex and across age groups. When using standard clinical definitions for hypertension, hypercholesterolemia, diabetes, and current tobacco use, antecedent prevalence of any traditional CVD risk factor remained nearly ubiquitous (~95%). The small proportion of CVD events that appeared to occur without clinically elevated risk factors often involved multiple traditional risk factors at levels above optimal but below diagnostic thresholds.

In an earlier study of 3 U.S. prospective cohorts—the Chicago Heart Association Detection Project in Industry, the Multiple Risk Factor Intervention Trial, and the Framingham Heart Study—exposure to at

FIGURE 4 Exposure to at Least 1 Nonoptimal Risk Factor Before CVD Events in MESA by Sex and Age at the Time of Event



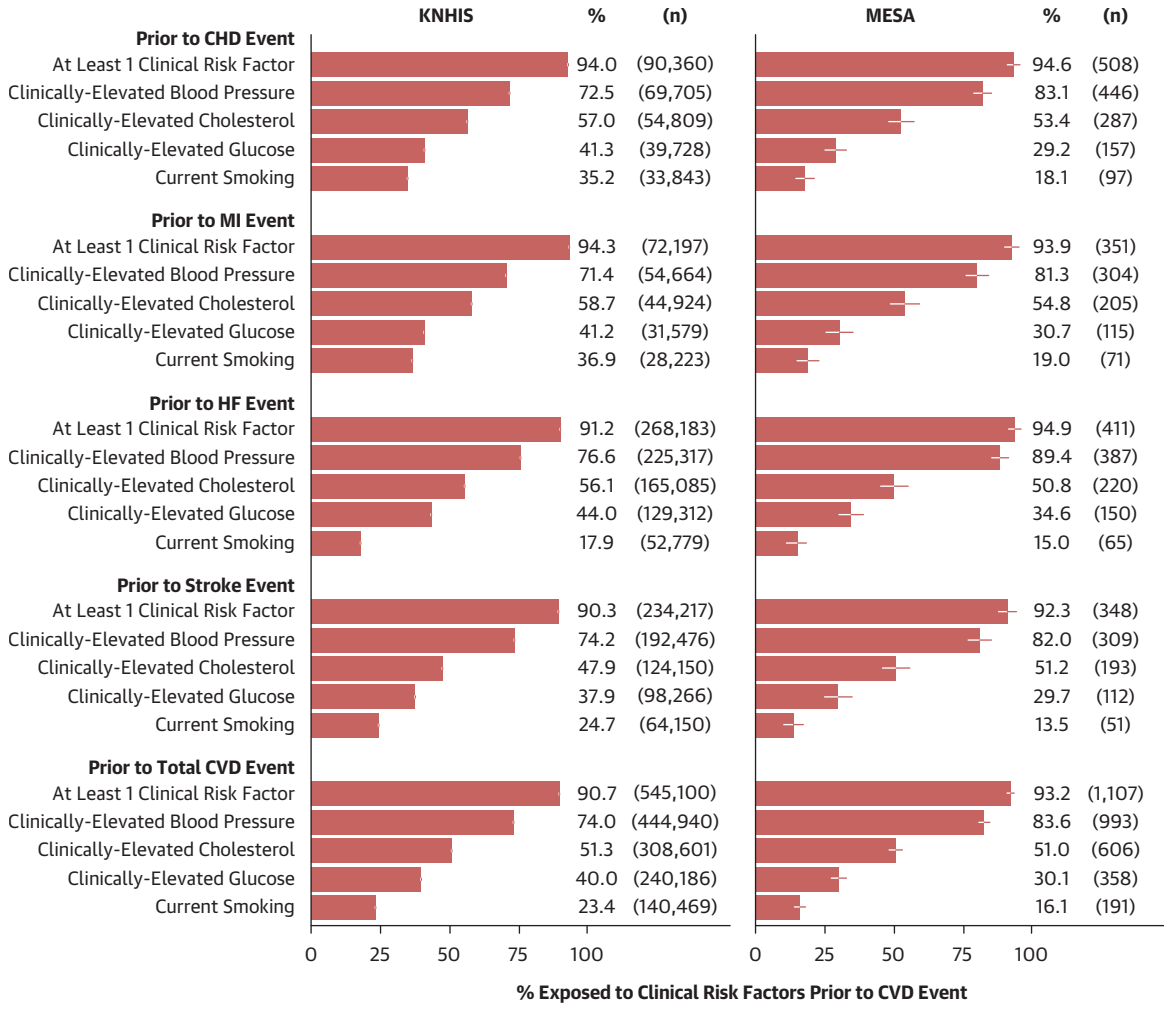
Data are presented as the number and % exposed to nonoptimal risk factors among the total number of events for each outcome and stratum. Horizontal error bars represent 95% CIs. Exposure to a nonoptimal risk factor was defined as systolic BP ≥120 mm Hg or diastolic BP ≥80 mm Hg or BP-lowering treatment; total cholesterol ≥200 mg/dL or lipid-lowering treatment; fasting glucose ≥100 mg/dL or diagnosis of diabetes or glucose-lowering treatment; or past or current tobacco smoking at any point among all available examination visits before the outcome event. Abbreviations as in Figure 1.

least 1 of the 4 traditional risk factors was 87% to 94% before MI or fatal CHD among individuals aged 40 to 59 years at baseline.[11] Nearly all (>99%) had at least 1 nonoptimal risk factor, when similarly defined as in our study.[11] Although these cohorts may reflect older data (1950s-1980s), more recent findings include 96% of MI patients from the ARIC (Atherosclerosis Risk in Communities) Study community surveillance (2000-2014)[24] and 96% of chronic CHD patients from the CLARIFY registry (Prospective Observational Longitudinal Registry of Patients with Stable Coronary Artery Disease) (2009-2010)[25] having at least 1 clinical risk factor. Because the current study extends these findings to events through 2022, the predominance of traditional risk factors before MI or CHD events likely persists in the contemporary global population.

In a post hoc analysis, we also observed that the prevalence of at least 1 traditional risk factor was high even among participants without clinical CVD events during the study follow-up, consistent with findings from the earlier 3 U.S. cohorts.[11] This is not surprising, because the high prevalence of these risk factors is well-established in the general population,[9,10] and exposure to ≥1 traditional risk factor may be necessary but not sufficient for CVD events to occur. Given such high background exposure, it is even less likely that patients with CHD would lack all traditional risk factors.

Taken together, our results challenge claims recently appearing in the medical literature that MI and CHD events occurring in the absence of antecedent major risk factors (SMuRF-less) are

FIGURE 5 Exposure to Clinically Elevated Risk Factors Before CVD Events



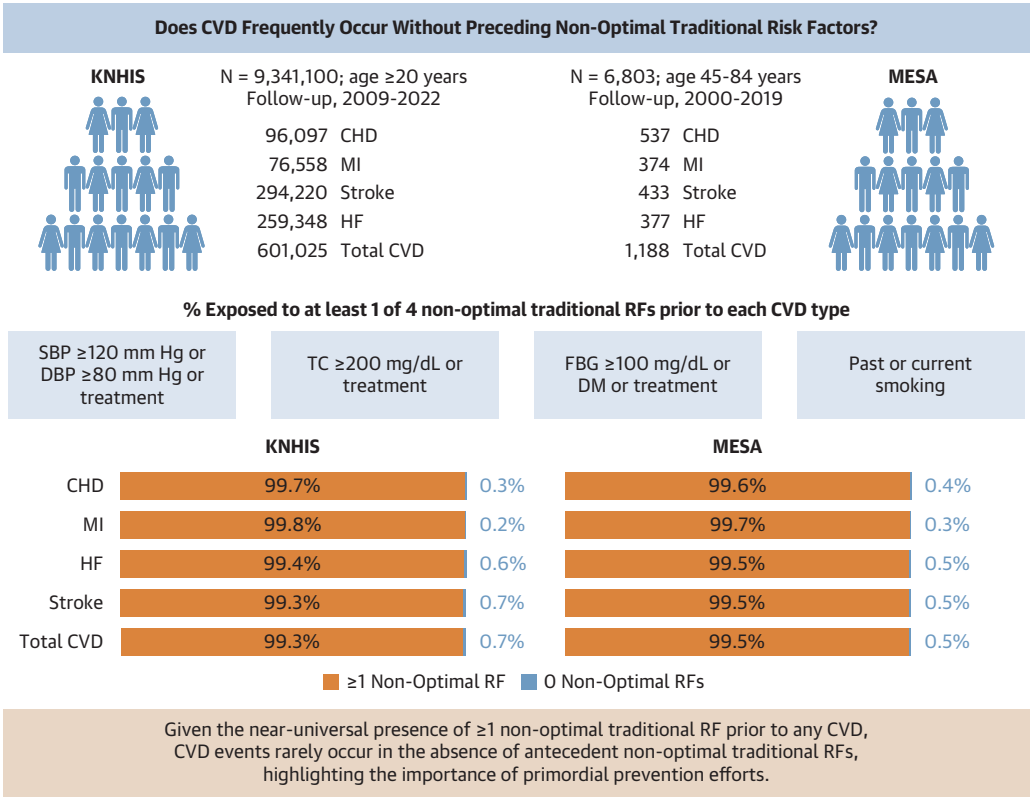
Data are presented as the number and % exposed to clinically elevated risk factors among the total number of events for each outcome. Horizontal error bars represent 95% CIs. For KNHIS, error bars may be too narrow to be visible. Exposure to a clinically elevated risk factor was defined as systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg or BP-lowering treatment; total cholesterol ≥240 mg/dL or lipid-lowering treatment; fasting glucose ≥126 mg/dL or diagnosis of diabetes or glucose-lowering treatment at any point among all available examination visits before the outcome event; or current tobacco smoking at the last examination before the outcome event. Abbreviations as in Figure 1.

increasingly common.[13,14] As antecedent risk factor exposures in those analyses were often defined by clinical diagnosis rather than repeated screening, their findings may reflect not absence of exposure but more likely: 1) missed diagnoses; or 2) exposure to risk factor levels below clinical diagnostic threshold but high enough to increase CVD risk in a continuous and cumulative manner.

Clinical hypertension, the most common modifiable risk factor preceding CVD events, is diagnosed only in 54% of affected individuals globally.[26] Low diagnosis rates have been documented also for hypercholesterolemia and diabetes.[27,28] The presence of undiagnosed and uncontrolled risk factors may also contribute to poor prognosis. The present study overcomes this limitation by leveraging cohorts with repeated, longitudinal assessments of risk factors (median, 4 times per participant), ensuring a more complete capture of prior exposures.

Each risk factor, particularly BP, cholesterol, and smoking, has a continuous, dose-dependent, and cumulative effect on CVD risk even below clinical diagnostic thresholds.[29-32] Similarly, prediabetes, not just diabetes, confers a higher CVD risk than normoglycemia.[33] Therefore, optimal levels of risk factors for preventing CVD are considered lower than

CENTRAL ILLUSTRATION Very High Prevalence of Nonoptimal Traditional Risk Factors Prior to Cardiovascular Disease Events



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CHD = coronary heart disease; CVD = cardiovascular disease; DBP = diastolic blood pressure; DM = diabetes mellitus; FBG = fasting blood glucose; HF = heart failure; KNHIS = Korean National Health Insurance Service; MESA = Multi-Ethnic Study of Atherosclerosis; MI = myocardial infarction; RF = risk factor; SBP = systolic blood pressure; TC = total cholesterol.

diagnostic thresholds used in clinical practice,[3-6] which contributed to the development of the AHA's concept of "ideal" CVH.[1] In the original Life's Simple 7, ideal CVH referred to untreated systolic BP <120 mm Hg and diastolic BP <80 mm Hg, untreated total cholesterol <200 mg/dL, untreated fasting glucose <100 mg/dL, and never-smoking (the same stricter cut points used in our study), as well as 3 more upstream lifestyle factors such as healthy diet, being physically active, and maintaining optimal body weight.[1] The updated Life's Essential 8 expands on this framework by adding a sleep metric and more granularity while maintaining similar optimal goals for the highest CVH scores.[7] The importance of achieving these stricter goals has been demonstrated by a markedly low incidence of CVD events and mortality associated with high CVH scores[23,34-36] as well as potential benefit of achieving them at the population level.[37] Nevertheless, it should be noted that no single cut point can definitively dichotomize a continuous risk factor into optimal vs nonoptimal, and that even stricter targets can be considered. For example, total cholesterol <200 mg/dL may not be sufficiently optimal by modern evidence, and LDL cholesterol <70 mg/dL or a lower-is-better approach is often pursued, particularly for secondary prevention.[38,39]

Although the idea of the SMuRF-less phenotype originated in the context of MI and acute coronary events, the broader question of how common the absence of traditional risk factors may be before any CVD event deserves more attention. It is widely recognized that HF and stroke share similar traditional risk factors and many risk reduction strategies

with CHD,[40,41] as also reflected in contemporary risk equations such as the ACC/AHA Pooled Cohort Equations[42] and PREVENT.[43] If these traditional risk factors were frequently absent before CVD events, it would imply that the current prevention strategies are partially missing novel drivers of CVD. Although the near-ubiquitous occurrence of nonoptimal traditional risk factors among CVD patients does not preclude the potential value of emerging, nontraditional risk factors as risk enhancers, it reaffirms the essential contribution of traditional risk factors to the development of CVD and their continued primacy as targets for prevention, given that CVD events rarely occur in their absence. Although the absence of nonoptimal risk factors is uncommon (<10%) in most populations,[9,10] other studies have shown that it is never too late to benefit from reoptimization, and the earlier the improvement, the better the outcomes.[7,23] Taken together, these findings reinforce the pursuit of primordial prevention strategies to prevent the development of risk factors, and the promotion of ideal CVH for the prevention of CVD events.

The strengths of this study include the use of binational, diverse, contemporary population-based cohorts with repeated longitudinal risk factor assessments and essentially complete follow-up of CVD events. The analyses of total and subtype-specific CVD events for antecedent risk factor exposures—using both clinical and lower optimal cut points—are highly relevant not only to questions regarding the SMuRF-less phenotype but, more importantly, to the broader understanding of CVH and its longstanding importance in the prevention of total CVD.

STUDY LIMITATIONS. First, despite repeated measurements of risk factors in both cohorts, missed exposures are still possible in persons with less frequent follow-up visits. Thus, the true exposure to risk factors could be even greater than what was observed in this study. Second, measurement errors in risk factors could have led to misclassification of exposure. As the effects of these risk factors on CVD are continuous and dose-dependent, the true risk factor burden is likely greater. Third, some participants (<5% in KNHIS and 1 individual in MESA among those with CVD) were excluded because of missing risk factor measurements. The potential overestimation of exposure, if any, should be negligible, as the excluded proportion is small, and true exposure among those excluded is also likely >99%. Fourth, this study did not assess other CVH factors, such as body weight, diet, physical activity, or sleep health. As antecedent exposure was already universal based on the 4 traditional physiologic risk factors currently studied, accounting for additional factors would not change the conclusion. Fifth, the outcome ascertainment in KNHIS was based on claims data with ICD-10 codes, which are potentially subject to misclassification.[19-21] If some of the CVD events were misclassified and were actually nonevents, which are likely associated with lower prevalence of antecedent risk factors, the true exposure would, again, be greater than observed in this study.

CONCLUSIONS

In this binational, diverse population-based cohort study, any CVD event—CHD, MI, HF, or stroke—was nearly universally preceded by exposure to at least 1 nonoptimal or clinically elevated level of 4 traditional risk factors, including elevated BP, elevated cholesterol, elevated glucose, and past or current smoking. CVD events rarely occur in the absence of these antecedent traditional risk factors.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.