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Reducing cardiovascular disease mortality and morbidity: Implementing cost-effective and sustainable preventive interventions

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Reducing cardiovascular disease mortality and morbidity: Implementing cost-effective and sustainable preventive interventions

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Editorial: Reducing cardiovascular disease mortality and morbidity: implementing cost-effective and sustainable preventive interventions

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Editorial on the Research Topic
Reducing cardiovascular disease mortality and morbidity: implementing cost-effective and sustainable preventive interventions

The global burden of cardiovascular diseases (CVD) is growing due to inadequate prevention and control of behavioral and metabolic risk factors, population growth, and aging (1). The CVD burden is highest in low-and middle-income countries with fragile health systems and financial and human resource constraints. There are very effective interventions that are affordable to all countries for addressing the cardiovascular epidemic (2). However, these interventions still need to be widely utilized (3). They include (1) public health policies to reduce behavioral risk factors, (2) access to integrated management of cardiovascular risk factors (hypertension, diabetes, hyperlipidemia, and other behavioral risk factors) and the mitigation of cardiovascular risk through a primary health care approach, and (3) universal health coverage of very cost-effective cardiovascular interventions including secondary prevention of heart attacks and strokes. The main aim of this Research Topic is to collate original research articles and reviews that provide insight into structural and contextual factors that impede the prioritization and uptake of affordable and sustainable interventions for CVD prevention and control.

Moyá-Amengual et al. evaluate the prevalence of elevated pulse pressure in an adult population in primary care and its association with other vascular risk factors, subclinical target organ damage, and CVD. Elevated pulse pressure was present in a quarter of the sample, and the prevalence increased with age. Raised pulse pressure was more frequent in men, patients with hypertension, CVD, and other target organ damage. These findings add to the body of evidence demonstrating that pulse pressure is an independent cardiovascular risk factor in the population over 60 years.

A healthy lifestyle, including physical activity, is featured as a key intervention for CVD prevention in this special issue. Su et al. investigate the associations of a healthy lifestyle with the subsequent development of CVD. During a 10-year follow-up of 51,929 participants, adherence to a healthy lifestyle pattern was associated with a lower risk of CVD, but this benefit was not as pronounced among normotensives as among hypertensives.

Zhou et al. conduct a meta-analysis to evaluate the effect of exercise on vascular function in patients with hypertension. Aerobic, resistance, and high-intensity intermittent exercise all significantly improved systolic blood pressure, diastolic blood pressure, and endothelium-dependent flow-mediated dilatation but not pulse wave velocity. More research is needed to investigate which exercise modality can improve hypertension-mediated vascular dysfunction and vascular sclerosis, and provide more effective exercise programs for hypertensive patients.

Eser et al. report an observational, longitudinal study to evaluate adherence to physical activity recommendations after percutaneous coronary interventions for coronary syndromes. They find that the moderate to vigorous physical activity recommendations of the World Health Organization physical activity guidelines can be fulfilled easily through activities of daily living without any planned or structured exercise. Future studies are needed to clarify how the recommendations are actionable for patient benefit.

This special issue includes the clinical trial protocol of a prospective study by Gonzalez-Jaramillo et al. that investigates the associations of objectively measured physical activity with major adverse cardiac events and mortality at 1-year follow-up after percutaneous coronary intervention.

Rosende et al. describe the results of a multi-country study designed for stepwise quality improvement of cardiovascular risk management, including hypertension control, using a primary health care approach. The aim was to identify improvement areas, reveal the challenges, and extend best practices for hypertension control and CVD risk management in primary health care. The study highlights many challenges to the prevention and control of CVD, for example, in the organization of health services including barriers to drug titration by non-physician health workers such as nurses and pharmacists. The authors also report a recurring concern from implementing countries that the treatment protocol of the study seemed too focused primarily on hypertension, although hypertension and diabetes have overlapping risk factors that lead to common pathways of complications and target organ damage. These findings highlight the dire need to promote a more integrated approach to address cardiovascular risk factors (hypertension, diabetes, hyperlipidemia, tobacco use, physical inactivity, and overweight) (4), secondary CVD prevention, and other common comorbidities such as depression and chronic kidney disease, particularly in primary care.

Indeed, the importance of using an integrated approach to address CVD that encompasses comorbidities is underscored by the study of Shen et al. They assess the relationship between the level of a person's depression and their risk of coronary heart disease, stroke, and all-cause and cardiovascular mortality, utilizing data from the United States National Health and Nutrition Examination Survey. They report a statistically significant association between depression and increased risk of coronary heart disease and stroke.

In addition to using integrated approaches in primary care, minimizing barriers to health system organization and access to essential medicines is critical for improving health outcomes. Pang et al. conduct a study in Yunnan Province, China, to assess the feasibility and impact of a nationwide healthcare service. They evaluate the accessibility and efficacy of basic public health care services by analyzing variables such as blood pressure, body mass index, lifestyle modification, and cardiovascular risk factors. The impact of the national basic public health care services program was evident in lowering risk factors for cardiovascular diseases, promoting healthy lifestyles, lowering blood pressure, increasing medication adherence, and the better control rate of hypertension.

Guo et al. analyze the effect of a full coverage policy of essential medicines on medication adherence. For patients with hypertension and diabetes, the full coverage policy of essential medicines in Taizhou, China, resulted in an increase in adherence to antidiabetic and antihypertensive medicines. These findings suggest that policymakers should consider removing cost-sharing for essential medicines as a promising strategy to improve medication adherence in people with non-communicable diseases, particularly in socially disadvantaged groups.

This Research Topic illustrates the breadth of research being undertaken regarding lifestyle, metabolic risk factors, primary health care, health systems, access to medicines, and Universal Health Coverage, in the prevention and management of CVD.

Author contributions

All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Objectively measured adherence to physical activity among patients with coronary artery disease: Comparison of the 2010 and 2020 World Health Organization guidelines and daily steps

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Background: Tailored recommendations for patients after percutaneous coronary interventions (PCI) need physical activity (PA) to be objectively measured and assessed for adherence to guidelines. The recent WHO guidelines removed the daily recommended bout duration, while the potential impact of this change on patients after PCI remains unclear.

Aim: We evaluated prevalence estimates of adherence to PA recommendations among patients after PCI across the 2010 [≥30 min moderate- to vigorous-intensity PA (MVPA) at ≥ 10-min bout duration] and 2020 WHO guidelines (≥30 min of MVPA of any bout duration), as well as 7,500 and 10,000 steps.

Methods: We conducted an observational longitudinal single-center study with patients after PCI for chronic or acute coronary syndrome (ACS); maximal age 80 years. Wrist-worn accelerometers recorded participants' PA data from the evening of hospital discharge over the next 18 days.

Results: We analyzed data from 282 participants with sufficient minimum wear time (7 days of ≥12 h), including 45 (16%) women; and 249 (88%) with ACS. Median wear time was 18 (17, 18) days. Median participant age was 62 (55, 69) years. Fifty-two participants (18.4%) fulfilled 2010 WHO guidelines and 226 (80.1%) fulfilled the 2020 WHO guidelines. Further, 209 (74.1%) participants achieved ≥7,500 steps/day and 155 (55.0%) performed ≥10,000 steps/day.

Conclusion: Among participants after PCI, most MVPA was accumulated in bouts <10 min, leading to a fourfold discrepancy between participants

fulfilling the 2010 and 2020 WHO PA recommendations. The number of steps/day may be a valid proxy to recent WHO PA recommendations as it is not dependent on the bout-length definition.

Clinical trial registration: [ClinicalTrials.gov], identifier [NCT04663373].

KEYWORDS

physical activity, guidelines, accelerometer, percutaneous coronary intervention, step counting

Introduction

Cardiovascular disease (CVD) remains the leading cause of death globally (1). Recent studies have found that lower levels of objectively measured physical activity (PA) were associated with higher rates of hospital readmission and adverse outcomes among patients after acute myocardial infarction, cardiac surgery, or decompensated heart failure (2–4). Similarly, daily steps have been associated with CVD risk factors and cardiometabolic outcomes (5, 6). In addition, a curvilinear relationship between PA volume and health benefits has been demonstrated, suggesting that the most significant reduction in morbidity and premature death were achieved with increases in PA among patients with coronary heart disease (CHD) (7) and healthy people at the lowest level in the spectrum of PA (8). A recent meta-analysis on PA trajectories among patients with CHD provided evidence supporting the benefits of maintaining or adopting an active lifestyle to improve survival and the possible harms of decreasing PA (9). For instance, compared to always-inactive patients, the pooled risk of all-cause mortality was 50% lower in those who remained active [HR (95% CI) = 0.50 (0.39–0.63)], 45% lower in those who were inactive but became active [0.55 (0.44–0.7)], and 20% lower in those who were active but became inactive [0.80 (0.64–0.99)] (9). PA is a foundational therapy for patients with CHD. Therefore, it is crucial to identify patients with low levels of PA, increase their PA, and facilitate a tailored cardiac care approach (10).

According to WHO's 2020 "Guidelines on Physical Activity and Sedentary Behaviour," adults should be physically active for 150–300 min per week with moderate intensity, 75–150 min per week with vigorous intensity, or an equivalent combination of the two to achieve substantial health benefits (11, 12). Moderate- to vigorous-intensity PA (MVPA) has been defined as a metabolic demand of greater than three times resting (3 METs) (12). PA is most commonly assessed by commercial accelerometers calibrated against measurements by metabolic carts so accelerations during activities with >3 METs are classified as MVPA (13, 14). Some calibration studies of accelerometers used steady-state activities, such as walking, running, and cycling, which require >3 METs when performed continuously for longer than 1–2 min when metabolism has reached a steady state (13, 14). When these accelerations occur for only a few seconds, they do not lead to energy consumption >3 METs. Therefore, WHO 2010 guidelines recommended performing MVPA in bouts of 10 min when the threshold of MVPA had to be reached 80% of the time. However, this bout requirement was lowered in the WHO 2020 guidelines because new evidence suggested that MVPA bouts <10 min also have beneficial effects on health and were associated with reduced all-cause mortality (15). The consequence of not requiring a minimal bout duration is that accelerations of single movements may be counted toward MVPA or a step count goal even if a person never exceeds 3 METs during an entire day. Therefore, the same volume and intensity of activities may result in varying minutes with MVPA when measured and analyzed by different commercial accelerometers whose algorithms are not available to the user.

Since walking is often the chosen exercise for people with heart disease, an alternative criterion to quantify PA is the number of steps; (6) steps per day is a practical PA measure because it is an easy-to-understand recommendation (16, 17). The commonly used artificial recommendation of 10,000 steps per day—promoted by a Japanese pedometer company in the 1960s (18)—was not based on scientific evidence, yet it has been used as the threshold value for providing health benefits in several studies (6, 19–22). Although achieving 10,000 steps/day was associated with meeting PA guidelines, (20) there is no conclusive evidence about how many steps per day are required for better health outcomes (16). For instance, Lee et al. found that hazard ratios associated with mortality continuously decreased with an increasing mean of daily steps among older women, leveling off at around 7,500 steps/day (16). Other studies supported a threshold of 7,500 steps per day for patients with cardiac conditions to reduce CVD risk factors, CVD morbidity, and mortality, as well as all-cause mortality (5, 6, 23).

For physically inactive patients with CVD, the usage of activity trackers has been recommended by the newest ESC guidelines for patients with CVD. However, using different evidence-based PA criteria may influence prevalence, therapy recommendations, and tools to promote PA among these patients. Therefore, comparing prevalence across guidelines may help determine actionable recommendations for patient

benefit. Thus, we evaluated prevalence estimates of adherence to PA recommendations across different guidelines among participants with coronary artery disease who recently underwent percutaneous coronary interventions (PCI) and wore a wrist accelerometer over 18 days after hospital discharge.

Materials and methods

Study population

Our study is a substudy of the Prognostic Impact of Physical Activity Patterns After Percutaneous Coronary Intervention (PIPAP) study (ClinicalTrials.gov identifier: NCT04663373)—a prospective observational single-center study that monitors patients' PA and assesses the potential of acceleration and steps parameters for risk quantification. The PIPAP study was approved by the Ethics committee of the Canton of Bern, Switzerland.

We recruited consecutive patients hospitalized for PCI after acute or chronic coronary syndrome (ACS, CCS) on their day of discharge or one day before discharge from December 2020 to March 2022. Substudy participants were provided with a wrist-worn accelerometer; a study information sheet, including an informed consent form; and a pre-addressed, prepaid envelope to return the signed consent form and accelerometer after the study period. Participants were asked to wear the accelerometer for 18 successive days starting from the evening of the day of their discharge from the hospital. We included patients who were aged <80 years and eligible for ambulatory cardiac rehabilitation, which *de facto* excluded patients who are frail or cognitively impaired. We also excluded study participants who did not record PA data for ≥7 days for ≥12 h.

Physical activity monitoring

Participants wore tri-axial accelerometers (Axivity AX-3, Axivity Ltd., Newcastle, UK) on their non-dominant wrist for 18 days. We programmed the devices using AX3 GUI V43 (24)—an open-source software—to record tri-axial accelerations of ±8 g at 50 Hz for 18 days starting on the evening of the day of the participant's hospital discharge. We chose 18 days to capture at least 14 days of PA data from participants who were transferred to another hospital before returning home. Transfer to another hospital usually delayed hospital discharge by 1–3 days.

Physical activity data processing

Using AX3 GUI V43, we downloaded PA data as continuous wave accelerometer (.cwa) files and then processed the PA data with the research-driven open-source R package GGIR (version 2.4.0) (25, 26). We derived participants' demographic (age and sex) and PCI data from the participating clinic's patient information system.

We calculated the movement component from the raw acceleration data using the default acceleration metric of the package—the Euclidean norm (vector magnitude) minus one (ENMO). It describes the raw tri-axial acceleration data conversion into an omnidirectional measure of body acceleration (27). The resulting ENMO values were expressed in gravity-based acceleration units [milligravity units (mg)] averaged over 5 s epochs.

We defined the following activity domains: <25 mg for inactivity; 25–99 mg for light PA; and ≥100 mg for MVPA, according to O'Donnell et al. (28). Sleep was also identified by the GGIR algorithm as documented and validated by van Hees et al. (29). Time spent in different PA domains was accrued in 1-min bouts. During analysis, we conducted autocalibration using local gravity as the reference, and we determined non-wear time over a window size of 60 min with a 15-min sliding window (30, 31).

While we derived activity parameters directly from GGIR, we determined steps by a Windowed Peak Detection open-source algorithm (Verisense_step_algorithm, last updated: 14.04.2021) based on Gu et al.'s (32) design and implemented for use in combination with the GGIR R package available on GitHub (33). We used validated input parameters for the step algorithm from a previous study of 22 participants during an outdoor physiotherapy session from the PIPAP study population (34).

Calculating parameters

We derived the following activity parameters from the GGIR package. First, the algorithm was set to calculate data from midnight to midnight. Next, we calculated the daily minutes with MVPA, inactivity, and sleep time. Further, we computed mean acceleration values in mg over each 24-h cycle. As Rowlands et al. recently suggested, (35) we determined minimal accelerations during the most active 2, 30, and 60 min in mg to compare with studies using different activity thresholds. We also calculated minutes in MVPA as bouts of at least 10 min with 80% of the 5 s epochs having accelerations over the MVPA threshold.

The step counting algorithm Verisense returned the number of daily steps for each valid day (i.e., wear time ≥12 h). Additionally, we calculated cadences for each minute from the meta-data Verisense derived, which included the number of steps for each 5 s epoch. We calculated the mean cadence over the whole 24-h cycle from these values. Moreover, we calculated daily minutes with ≥100 steps/min and 0 steps/min (5). We also determined mean cadences for the most active 1, 30, and 60 min, as proposed by Tudor-Locke et al. (36). We summarized

all parameters as the mean of each participant's overall valid days and the median of all participants.

Statistical analysis

We performed all analyses with R Studio (Version 1.4.1106-5). We calculated descriptive statistics reporting the number of participants and percentages of all participants and medians with first and third quartile for continuous activity parameters due to their primarily non-parametric distribution. We performed linear regressions for MVPA based on 1-min bouts and MVPA based on 10-min bouts with daily steps using the lm function. We calculated the proportions of adherence to the 2010 and 2020 WHO guidelines and daily steps for the total sample and for subgroups according to sex, median age of the sample (<62 versus ≥62 years old), and clinical presentation of the disease (ACS versus CCS).

Results

Study participants

Of the 916 patients who met inclusion criteria within our 16-month recruitment period, 369 patients (40.3%) agreed to participate in the study (Figure 1). We excluded 87 of those 369 participants. During the observational period, two participants (0.5%) died before completing 7 days of wear-time; ten participants (2.7%) never returned the accelerometer, and nine participants (2.4%) never wore the accelerometers. Twenty-seven additional participants met exclusion criteria: 10 participants had <7 days of ≥12-h wear time, four participants were aged >80 years, and 13 participants (3.5%) did not send the informed consent forms. Seven (1.9%) participants' accelerometers had insufficient battery power. Devices of 25 participants had not yet been sent back and received by us. This resulted in 44 patients (11.9%) who were non-compliant with the study protocol. Consequently, we performed our data analysis with 282 valid recordings (76.4%).

Of the 282 participants with valid recordings, the median age was 61.5 (first quartile 55, third quartile 69) and 46 (16.1%) were women (Table 1). Thirty-three participants had CCS and 249 participants had ACS (88.3%). A third of all participants started recording on day 1 after PCI (PCI was on day 0), the majority started recording on the second day (75.9%) and by day 3 88.7% had started their recording. Therefore we included all recorded days as of day 2. The median number of days of device wear time ≥12 h was 18 (17, 18), and most participants (79.4%) still recorded day 18, while only 48.9% of patients still recorded

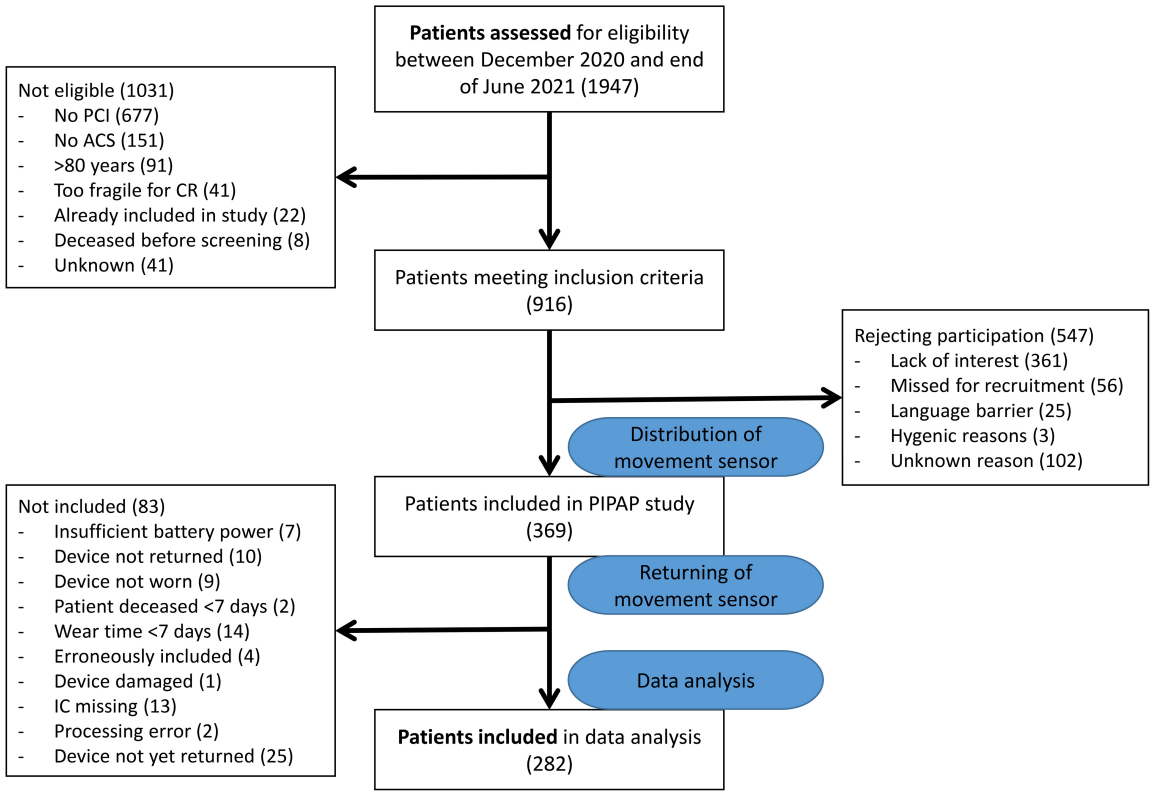

FIGURE 1
Patient flow.

TABLE 1 Activity parameters of groups according to different gradients in MVPA and mean time spent in MVPA.

Group	All patients		2020 WHO guidelines (MVPA ≥30 min)		2010 WHO guidelines (MVPA ≥30 min, bouts ≥10 min)		Steps ≥7,500		Steps ≥10,000	
Number of patients	282		226		52		209		155	
Number of female patients (%)	45 (16.1)		34 (15.0)		4 (7.7)		33 (15.8)		27 (17.4)	
Age (years)	61.5	(55, 69)	61	(54, 68)	60	(55, 67)	61	(55, 68)	61	(56, 69)
LPA time (min/day)	242	(193, 293)	255	(213, 303)	259	(223, 296)	260	(224, 303)	274	(240, 318)
MVPA time (min/day)	57	(33, 82)	67	(48, 93)	105	(76, 147)	71	(51, 95)	79	(60, 104)
MVPA time of bouts ≥10 min (min/day)	7.1	(1.0, 22.2)	11.3	3.4, 26.4)	45	(36, 70)	12	(4, 27)	13.7	(5.4, 32.9)
Vigorous physical activity (min/day)	0.5	(0.1, 1.1)	0.7	(0.3, 1.3)	0.9	(0.5, 1.5)	0.7	(0.3, 1.3)	0.8	(0.4, 1.4)
Inactive time (min/day)	721	(628, 812)	699	(617, 770)	625	(575, 721)	688	(613, 766)	655	(602, 739)
Sleep time (min/day)	414	(346, 468)	421	(346, 469)	436	(359, 470)	415	(348, 465)	421	(349, 465)
Mean acceleration per 24 h (mg)	19.8	(15.8, 25.7)	22	(18, 27)	27	(22, 32)	23	(19, 27)	24	(21, 28)
Minimal acceleration during 2 most active minutes (mg)	273	(211, 333)	295	(244, 351)	311	(271, 377)	300	(246, 354)	314	(257, 368)
Minimal acceleration during 30 most active minutes (mg)	127	(103, 152)	136	(117, 160)	171	(150, 186)	139	(122, 163)	145	(130, 170)
Minimal acceleration during 60 most active minutes (mg)	97	(77, 120)	106	(90, 126)	137	(122, 153)	107	(92, 127)	114	(101, 131)
Daily steps (steps/day)	10,463	(7391, 13837)	11,966	(9,594, 14,925)	15,036	(11,702, 19,008)	12,186	(9,986, 15,047)	13,427	(11,833, 15,875)
Mean cadence per 24 h (steps/min)	7.2	(5.1, 9.5)	8.2	(6.6, 10.3)	10.5	(8,1, 13.1)	8.4	(6.9, 10.4)	9.3	(8.1, 11)
Cadence ≥100 steps/min (min/day)	8.7	(2.4, 18.3)	11.5	(4.2, 20.9)	32	(19, 49.6)	12.1	(4.5, 21.5)	13.8	(5.8, 28)
Time with cadence = 0 (%)	69	(64, 75)	68	(63, 72)	65	(62, 71)	67	(62, 71)	64	(61, 68)
Cadence of most active minute (steps/min)	106	(100, 112)	108	(103, 113)	113	(109, 117)	109	(104, 114)	110	(106, 114)
Cadence of most active 30 min (steps/min)	83	(72, 94)	88	(79, 96)	101	(95, 106)	89	(80, 97)	92	(84, 100)
Cadence of most active 60 min (steps/min)	72	(60, 83)	77	(67, 86)	93	(85, 99)	78	(69, 86)	82	(73, 90)

Parameters are indicated as group medians and first and third quartiles (in brackets) based on patients' means over the measuring period. Inactive time: minutes with accelerations <25 mg; MVPA (moderate to vigorous physical activity): minutes with acceleration ≥100 mg.

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day 19 after PCI. Between day 3 and day 18, data was available for at least 87.9% of all patients.

Daily activity measurements

When expressed as mean daily activity over the 18 days, 226 participants (80.1%) had ≥30 min of MVPA on an average day (**Table 1**). However, only 52 (18.4%) study participants spent at least 30 min in MVPA with bouts of ≥10 min, thus fulfilling 2010 WHO PA guideline recommendations. The median duration of all participants' mean MVPA time was 57 (33, 82) minutes, and the median of each participant's mean time in bouts ≥10-min MVPA was 7 (1, 22) minutes. Median sleep time was 6.9 (5.8, 7.8) hours, and median inactive time was 12.0 (10.5, 13.5) hours. One-hundred-and-fifty-five participants (55.0%) reached ≥10,000 steps/day, and 209 (74.1%) performed ≥7,500 steps/day. Two-hundred-and-four participants (72.3%) reached a cadence of ≥100 steps/min during the most active minute of the average day. Over the most active 30 min, this cadence was reached by 38 participants (13.5%), and over the most active 60 min, 12 participants (4.3%) reached this threshold.

On day 2 after PCI, 43.5% of participants with available data on that day fulfilled the MVPA criterion of at least 30 min according to 2020 WHO PA guidelines. This percentage increased steadily until day 7, after which it decreased again slightly (**Figure 2**). A similar percentage of participants fulfilled the criterion of a minimum of 7,500 steps/day. The minimum recommendation of 30 min of MVPA in ≥10-min bouts according to the 2010 WHO guideline was fulfilled by 8.9% on the second day and increased steadily until day 17 when 23.4% fulfilled this criterion. On day two, 28.5% reached 10,000 steps/day and by day 17, 61.3% had reached 10,000 steps/day.

Linear regressions for moderate- to vigorous-intensity physical activity and daily steps

The linear regression of daily mean steps with daily mean MVPA according to the 2020 PA guidelines explained 47.5% of the total variability (r = 0.69, p < 0.0001), while the linear regression of daily mean steps with daily mean MVPA according to the 2010 PA guidelines explained only 13.6% (r = 0.37, p < 0.0001, **Figure 3A**). Approximately 2,500 steps corresponded to 0-min MVPA per 2020 WHO guidelines, and 5,000 steps corresponded to 0-min MVPA per 2010 WHO guidelines. The intersection of the regression line with 30 min of daily MVPA according to 2020 WHO guidelines corresponded to 6,250 daily steps, while more than 15,000 steps on average were necessary to reach the 30-min threshold according to 2010 WHO guidelines. Similar observations could be made

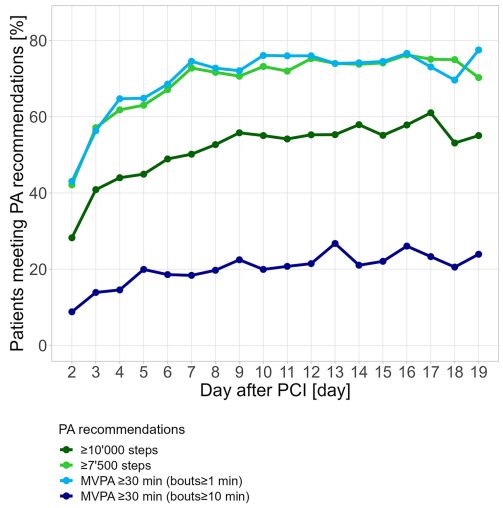

FIGURE 2
Percentage of participants reaching various criteria for PA after hospital discharge for PCI. PCI was performed on day 0. Fulfillment of PA criteria was calculated for each participant and each day individually.

for the linear regression models of the daily mean cadence of the most active 30 min with daily mean MVPA according to the 2010 and 2020 WHO guidelines (**Figure 3B**). The linear regression models for mean cadence with MVPA according to the 2010 guidelines explained 29.1% of the total variance (r = 0.54, p < 0.0001) and only 16.8% (r = 0.41, p < 0.0001) with MVPA according to the 2020 guidelines. The intersection of the regression line with 30 min of daily MVPA per 2020 WHO guidelines corresponded to 60 steps/min, while a cadence of 100 steps/min was observed for reaching the 30-min threshold according to 2010 WHO guidelines.

Adherence to guidelines and steps per day according to age, sex, and coronary artery disease presentation

Overall, we found that most of the proportions of adherence did not statistically differ across categories of age, sex, and disease presentation at the PCI (**Table 2**). However, the lowest adherence to the 2010 WHO guidelines was observed among women (8.9%), and patients older than 62 years had a lower proportion (74.5%) of adherence to the 2020 guidelines, compared to the patients in the younger group (86%).

Discussion

After recent PCI, PA assessment with wrist-worn accelerometers among our participants was found to be highly feasible with a participation rate of 40 and 87% compliance. We

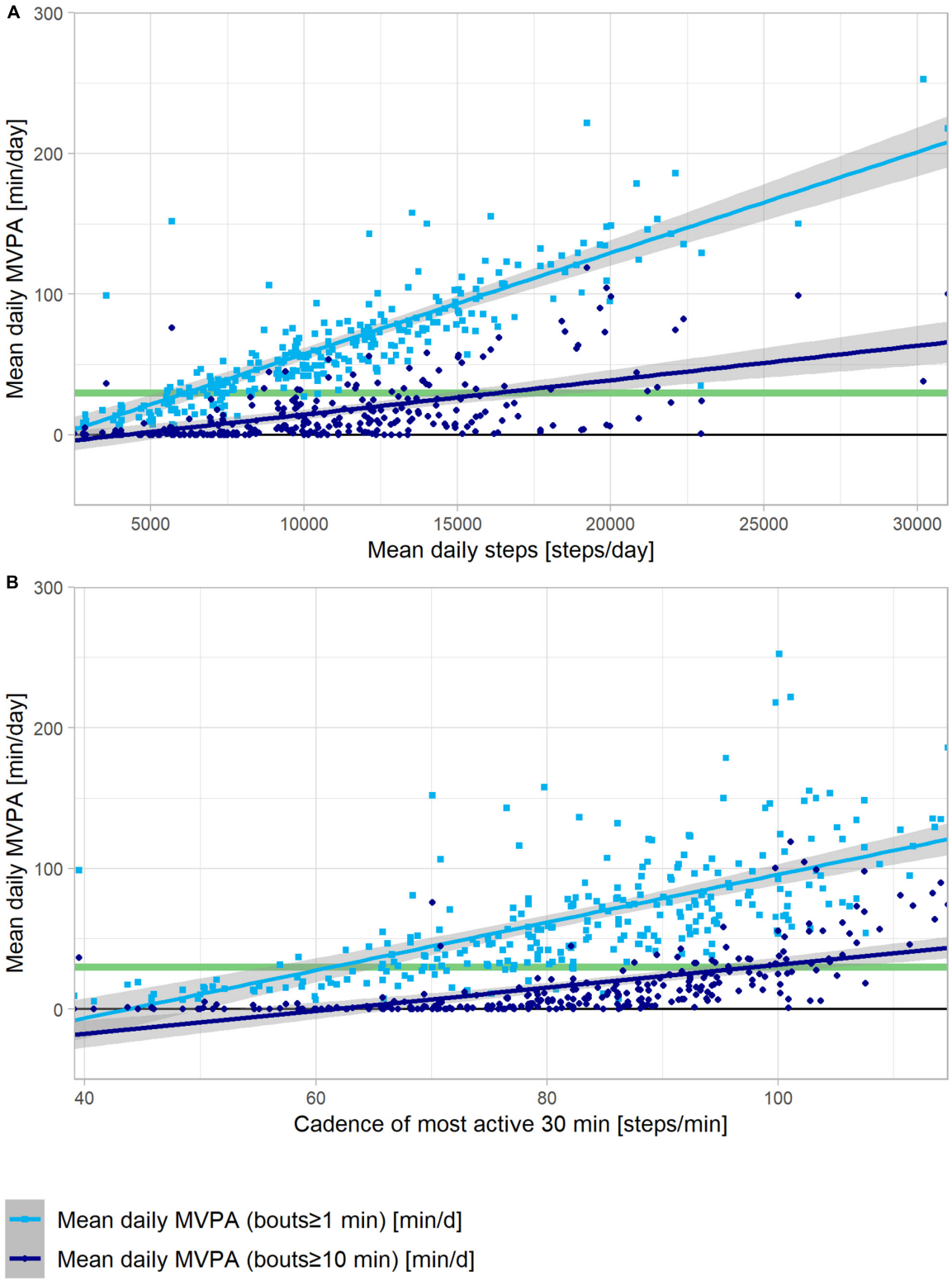

FIGURE 3
Linear regressions of MVPA in bouts of ≥1 min (light blue squares) and ≥10 min (dark blue dots) versus steps per day **(A)** and versus step cadence of the 30 most active minutes of each day **(B)**. Each data point reflects mean values over the 18 days for each patient. The 95% confidence interval is depicted by the gray area around the regression lines.

TABLE 2 Results of adherence to guidelines and steps per day according to age, sex, and disease presentation.

	Total sample	Age groups		Sex		Coronary disease presentation	
		<62	≥62	Male	Female	ACS	CCS
Number of patients [*n* (%)]	282	141 (50)	141 (50)	237 (84)	45 (16)	249 (88)	33 (12)
Adherence to guidelines and daily steps [*n* (%)]							
WHO 2020 guidelines	226 (80.1)	121 (86)	105 (74.5)*	192 (81)	34 (75.6)	202 (81)	24 (73)
WHO 2010 guidelines	52 (18.4)	31 (22)	21 (15)	48 (20.3)	4 (8.9)*	44 (18)	8 (24.2)
Steps ≥7,500	210 (74.5)	110 (78)	100 (71)	177 (74.7)	33 (73.3)	186 (74.7)	24 (73)
Steps ≥10,000	154 (54.6)	77 (54.6)	77 (54.6)	127 (53.6)	27 (60)	136 (54.6)	18 (54.5)

n, number of participants; ACS, acute coronary syndrome; CCS, chronic coronary syndrome; WHO, World Health Organization. Percentages are based on the population for each column.
*p-value < 0.05 for the comparison between groups of age, sex, and coronary disease presentation.

found a wide variation in the prevalence of sufficient activity according to WHO PA guidelines from 2010 and 2020, namely spending 30 min in MVPA with or without 10-min bouts. While only 18% of our participants fulfilled 2010 WHO guidelines with MVPA counted only as bouts lasting at least 10 min, 80% met the recommendations from the 2020 WHO guidelines. A higher median number of daily steps and more daily min at a cadence ≥100 steps/min was found among participants who reached the average of 30-min MVPA in 10-min bouts when compared to participants who only met the recommendations from the 2020 WHO guidelines (**Figure 4**).

To our knowledge, this study is the first to quantify the discrepancy between the achievement of PA recommendations with and without the 10-min bout requirement in patients after PCI. Our findings are consistent with other studies conducted on different populations. For instance, a cross-sectional study investigating data from the 2003–2004 National Health and Nutrition Examination Survey (NHANES) (37) and a study on data from the Framingham Heart Study (38) also reported a fourfold discrepancy, whereas a study on a subsample of the NHANES population found a sixfold discrepancy (39). The 2020 WHO guideline was based on studies claiming that bouts shorter than 10 min of MVPA were also associated with reduced all-cause mortality in the general population (15). However, the majority of those studies supporting the health benefits of PA accumulated in bouts of <10 min in duration used a cross-sectional design, with none of the randomized studies reporting on the effects of PA accumulated in bouts of <10 min. Other studies established associations of MVPA acquired sporadically or in bouts ≥10 min with some cardiovascular risk factors. For instance, a study of >1,000 Canadian adults wearing hip-worn tri-axial accelerometers, reported that the time of MVPA with bouts ≥1 min was nearly double the time of MVPA with bouts ≥10 min (40). The presence or absence of metabolic syndrome was equally well discriminated by bouted (≥10-min) or sporadic (1–9 min) MVPA (40). Similar associations of CVD factors with MVPA bouts duration were found in a sample of >2,000 participants from the Framingham Heart Study (38). In another study of over 6,000 adults from the NHANES study, MVPA in bouts and non-bouts were similarly associated with cardiovascular risk factors (37); however, a study among the subpopulation of adults younger than 65 years from the Canadian health measures survey found a four times greater inverse association of obesity with MVPA in bouted compared to sporadic MVPA (39). The Coronary Artery Risk Development in Young Adults (CARDIA) study of approximately 2,000 healthy adults found that accumulating sporadic MVPA, independently of bouts, was a protective factor against the development of hypertension but not against obesity (41).

Bouts of 10 min or longer are likely to represent planned and structured exercise, while shorter bouts more likely reflect activities of daily living. Likewise, the median time with a cadence ≥100 steps/min of our study participants was 8 min/day, indicating many of our participants barely reached this cadence. Hence, most of our participants' steps were performed at low cadences or in bouts shorter than 1 min, which again suggests activities of daily living rather than physical exercise increasing heart rates and cardiac output. In our study, the proportion of participants fulfilling the 2020 WHO PA guidelines was slightly higher than the proportion of participants walking ≥7,500 steps/day—a threshold found to discriminate between cardiovascular risk factors (6). The percentage of participants walking ≥10,000 steps was between the proportions of participants fulfilling the 2010 and 2020 WHO PA guidelines. Unlike MVPA, people can easily verify the number of steps calculated by an accelerometer device by walking a predefined number of steps or by walking at a certain cadence for a defined time. Not only can the number of steps be verified, but it is also an easily followed recommendation, such as walking 3,000 steps or walking at brisk 100 steps/min for 30 min.

It is questionable whether PA of very short duration has the same beneficial effects on patients with CVD as structured exercise. Several mechanisms may explain the known benefits associated with PA in patients with CVD, including endothelial

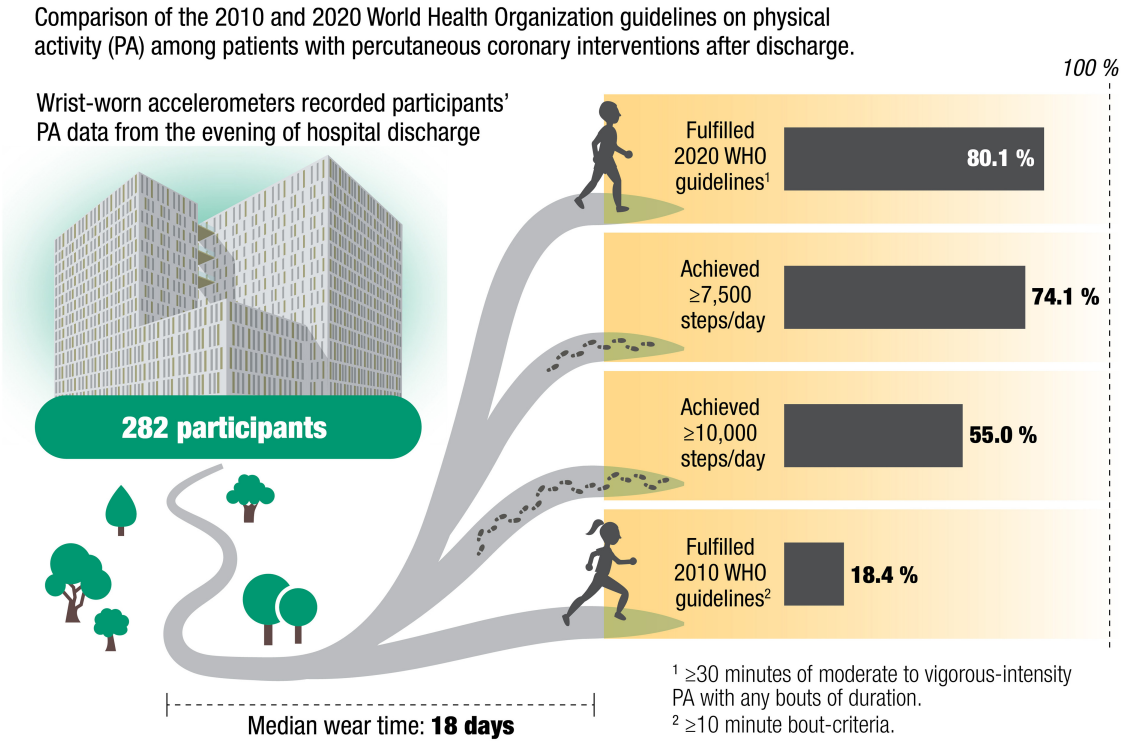

FIGURE 4
Illustration of fraction of patients reaching 2020 versus 2010 World Health Organization guidelines on physical activity, as well as those reaching 7,500 and 10,000 steps per day.

function improvement (42, 43) and antiatherosclerotic (43, 44) and anti-inflammatory (45) effects. Traditional risk factors for CHD such as diabetes, hypertension, smoking, and hypercholesterolemia are associated with endothelial dysfunction, which in turn results in impaired nitric oxide production, abnormal vasoconstriction, chronic inflammation, and increased oxidative stress (46). Endothelial dysfunction, inflammation (47), and oxidative stress (48) play an important role in both the pathogenesis and prognosis of CVD. Against this background, PA increases beneficial shear stress at the vessel wall, down-regulates the expression of the angiotensin II type 1 receptor (49), and decreases NADPH oxidase activity and superoxide anion production, which in turn decreases the generation of reactive oxygen species and inflammation while preserving endothelial nitric oxide bioavailability and its protective anti-atherosclerotic effects (50). Conversely, physical inactivity increases vascular NADPH oxidase activity and increases vascular reactive oxygen species generation, which in turn contributes to endothelial dysfunction and atherosclerosis (51). Exercise training of distinguished volume and intensity has proven beneficial effects on endothelial function and arterial stiffness (52, 53). At least for weight loss and prevention of obesity, bouts ≥10 min have been suggested as necessary (39, 41, 54). Future studies need to clarify how recommendations are actionable to patient benefit and whether daily step targets for patients after PCI gauge prognostic importance.

Limitations

Some limitations may affect our study. First, inactive and uninterested patients may have been lost during recruitment since participants' consent required their willingness to wear an accelerometer. Consequently, our study participants may be more active and compliant than typical patients after PCI in clinical settings. With a 40% inclusion rate, it is possible that our study included a higher percentage of physically active patients whereas inactive patients could have refused participation. However, after the recommendation for monitoring objective PA that has been recently endorsed by the ESC, (55) the inclusion process for this and any other future studies is expected to improve. Specifically in our setting, the use of accelerometer is now a standard of care. All patients are recommended to wear the accelerometer for 18 days after hospital discharge from PCI and together with their general practitioners receive their analyzed data and PA recommendations upon returning the device.

Our recruitment team did not enlist patients who did not qualify for ambulatory cardiac rehabilitation because

they were too frail or cognitively impaired. Therefore, our results may have been affected by selection bias. However, selection bias did not affect the large discrepancy between the number of participants satisfying 2010 versus 2020 WHO PA guideline criteria, which was our main aim. Second, the median MVPA of 1-min bouts among our study participants was 57 min/day or 399 min/week, fulfilling or even exceeding the recommended range of 150–300 min/week. It is possible that PA measured in our study overestimated PA levels due to the Hawthorne effect since pedometer use has been shown to increase patients' PA (19, 22). Wrist-worn accelerometers might also underestimate activities, such as cycling (56). In contrast, activities involving arm movements may overestimate PA levels since the metabolic cost of arm movements is smaller than that of leg movements due to the smaller muscle mass involved in the effort (57). However, since walking is one of the most frequently reported leisure time activities worldwide, this limitation may be negligible (58), especially among patients with cardiac conditions (6).

Third, since most PA data are averaged over 1-min windows, dropping the criterion of 10-min bouts means that bouts as few as 1 min are sufficient for qualifying as MVPA in the 2020 WHO guidelines. However, with many proprietary devices, the minimal bout length is not obvious to the user, and some devices use 15 s or even 5 s epochs (59). The choice of epoch length also affects the calculated daily time spent with MVPA. MVPA time was doubled when epoch length was increased from 4 to 20 or 60 s in a study using hip-worn uni-axial accelerometers (60). Unless a device with a defined wearing location, data sampling rate, epoch duration, and algorithm settings for calculation of MVPA is validated against energy consumption measured by a metabolic cart, it is impossible to know whether time with MVPA is actually time with an energy consumption $\geq$3 METs.

Our data imply that tracking the global target set by WHO to reduce inactivity by 2025, should take into consideration the discrepancy of values that are consistently reported in the literature. Using the new guidelines to evaluate policies supporting PA in settings where baseline PA levels were measured through different criteria, may be biased and not reflect the reality of the expected change. Finally, whether CV risk can be equally reduced by MVPA with and without the 10-min bout requirement in patients after PCI needs to be investigated in future studies, such as the PIPAP study. Since the identification of MVPA is highly dependent on the duration of analyzed bouts and consequently varies between accelerometer devices and algorithm settings, a target number of steps may be more manageable, understandable, and feasible for people.

Conclusion

This study found a fourfold discrepancy in the frequency of participants fulfilling 2010 and 2020 WHO guidelines for PA among patients following hospital discharge after PCI. In this setting, the recommendations from the 2020 WHO PA guidelines for MVPA were fulfilled easily by activities of daily living, without any planned or structured exercise. Future studies need to clarify how recommendations are actionable to patient benefit and whether daily step targets for patients after PCI gauge prognostic importance.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethikkommission des Kantons Bern. The patients/participants provided their written informed consent to participate in this study.

Author contributions

NG-J, AB, OF, and MW designed the study. PE, SW, RF, and JF were involved in data collection, processed the data, and performed data analyses. PE, SW, and NG-J drafted the manuscript. All authors approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Prognostic impact of physical activity patterns after percutaneous coronary intervention. Protocol for a prospective longitudinal cohort. The PIPAP study

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Introduction: Current guidelines recommend wearable activity trackers to detect insufficient physical activity (PA) and help increase PA to prevent or ameliorate cardiovascular disease. However, there is a paucity of data regarding how objectively measured PA trajectories, patterns, and sedentary time, are associated with mortality and recurrent events after percutaneous coronary intervention (PCI) in patients with established coronary artery disease (CAD). Additionally, it remains unclear if early PA and sedentary time after PCI are associated with such outcomes. Therefore, in the present study (ClinicalTrials.gov Identifier: NCT04663373), we aim to establish the associations of objectively measured PA with major adverse cardiac events and mortality at one-year follow-up.

Methods and analysis: In this single-centre observational study, patients with CAD will be prospectively recruited immediately after PCI. All the information from the clinical history, baseline characteristics, and outcomes during follow-up will be obtained from the CARDIOBASE registry. Accelerometer data will be collected for 18 days following hospital discharge and 14 days at one-year follow-up. PA trajectories will be identified by group-based trajectory modeling. Major adverse cardiac events and mortality will be prospectively monitored up to 1 year after PCI. All data will be collected using Research Electronic Data Capture.

KEYWORDS

cohort, protocol, prevention, coronary disease - epidemiology, accelerometer

Introduction

Coronary artery disease (CAD) is the leading cause of cardiovascular disease (CVD) mortality (1, 2). Lifestyle physical activity (PA) and exercise-based cardiac rehabilitation (CR) successfully reduce the risk of CVD morbidity and mortality and improve the quality of life in patients with CAD (3–5). American and European guidelines (6, 7) thus recommend CR and PA for patients with acute and chronic coronary syndromes, particularly those who undergo percutaneous coronary intervention (PCI) (8).

The use of accelerometers provides objective, feasible, and reliable PA data across its spectrum, including sedentary time, activity counts (divided into time spent in light, moderate and vigorous activity), daily steps, and sleep (9). Some evidence has provided insights into the associations of objectively measured PA and short-term prognosis after hospital admission in patients with CVD. For instance, the number of steps during the three last days of hospital stay after coronary artery bypass grafting is a strong predictor for 30-day cardiac rehospitalization (10). Likewise, in patients hospitalized for decompensated heart failure, physical inactivity within the first week after hospital discharge is associated with 30-day hospital readmission (11).

Current guidelines recommend wearable activity trackers as a tool that may help increase PA (12). However, there is a paucity of data regarding how objectively measured PA patterns and sedentary time are associated with mortality and recurrent events after PCI in patients with CAD. Additionally, it remains unclear if an early increase in PA and a decrease in sedentary time after PCI is associated with such outcomes at 1-year follow-up. Therefore, in the present study (ClinicalTrials.gov Identifier: NCT04663373), we aim first to quantify PA levels, sedentary time, and PA trajectories in participants wearing an accelerometer for 18 days starting on the day of their hospital discharge and for 14 days on 1 year of follow-up. We also aim to evaluate how PA, sedentary time, and PA trajectories early after PCI are associated with major adverse cardiac and cerebrovascular events (MACCE) and 1-year mortality in patients with CAD. Through the extension of the current knowledge and understanding of the role of PA in the prognosis of CAD, these results could enhance cardiovascular health and clinical practice. Our study could emphasize the importance of objectively measured PA and sedentary time as a standard-of-care evaluation in patients with CAD to contribute to clinical decision-making, design tailored interventions and perhaps establish a prognosis.

Objectives

Among patients with CAD who underwent PCI, we aim to establish the association of objectively measured PA and sedentary time with mortality and MACCE at 1-year follow-up.

The aim will be addressed *via* specific objectives:

(1) Determine the correlation between objectively measured PA, daily step counts, step cadence, inactivity time and sleep time over the 18 days following hospital discharge after PCI and over 14 days at 1-year follow-up.
(2) Compare PA, steps and inactivity between patients subsequently performing CR with patients not performing CR.
(3) Identify PA components and PA trajectories associated with mortality and the first occurrence of MACCE at 12 months.
(4) Identify factors that are associated with different PA trajectories from the immediate period following PCI to 1-year follow-up.

Methods and analysis

Study design and setting

We will conduct an observational, longitudinal monocentric study with a prospective collection of data from the University Hospital of Bern (Inselspital).

Population

Consecutive adult patients with acute or chronic coronary syndrome who underwent PCI.

Selection criteria

Inclusion criteria

(1) Men and women older than 18 years after treatment with PCI for chronic or acute coronary syndrome.
(2) Willingness to participate in the study.

Exclusion criteria

(1) No adequate understanding of how to wear the accelerometer.
(2) Behavioral or cognitive disorders are sufficient to interfere with the patient's ability to comply with the protocol instructions or follow-up procedures.
(3) Frailty or extensive nursing care needs.
(4) Major surgery, including implantation of cardiac devices, or major neurologic events and cerebrovascular events, within 30 days before screening.

(5) Planned major surgery within the next 20 days after PCI, including staged cardiac surgery.

Sample size calculation

The sample size was calculated based on the available information from the CARDIOBASE registry regarding the proportion of incident cardiovascular events among CAD patients undergoing PCI. The Schoenfeld formula was utilized for survival analysis. Based on the data from the CARDIOBASE registry, we assumed that the proportion of MACCE events within 1 year after the PCI procedure would be 9% (13). We assumed that the physically active patients in the present study would have a 50% reduction in the 1-year risk of incident MACCE, compared to the inactive ones (14). To obtain a power of 80% and a precision of 5%, we estimated a sample size of 726 participants.

Exposures, outcomes, and covariates

Exposures

(a) Each component of the continuum of PA, including sedentary behavior, light, and moderate to vigorous (MVPA) levels of activity, and sleep. Further, the number of daily steps and step cadence.
(b) Trajectories of PA parameters (as stated above) in the short-term (18 days after hospital discharge) and the long-term (hospital discharge to 1-year follow-up).

Outcomes

(a) Main outcomes: (a) MACCE. In line with previous literature on CVD prevention (15), the definition of MACCE will include ischemic endpoints as cardiovascular death, myocardial infarction, stent thrombosis, and stroke; and revascularization endpoints as target lesion revascularization and target vessel revascularization; (b) All-cause mortality.
(b) Secondary outcomes: Individual components of MACCE.

Covariates

(a) Demographic factors: Sex, age, marital status, zip code.
(b) Clinical factors: Personal history of diabetes, dyslipidemia, hypertension, smoking, alcohol intake, body mass index, and CAD presentation at PCI (acute vs. stable), CR attendance.
(c) Procedural-related factors: Number of affected vessels, number of stents, presence of left main disease, and staged angioplasty.

Protocol activities

Consecutive patients who have been hospitalized for percutaneous coronary intervention (PCI) after acute or chronic coronary syndrome (ACS, CCS) will be recruited on the day of discharge or one day before discharge by a team of nurse practitioners who see the patients and inform them about available CR programs. Patients who consider participating will receive a wrist-worn accelerometer, a patient information sheet including an informed consent form and an addressed and prepaid envelope to return the signed consent form and the accelerometer after the study period. They will be asked to wear the accelerometer for 18 days starting from the day of discharge from the hospital. At discharge, the patient will start wearing the accelerometer according to the instructions given by the research team. Patients undergoing staged PCI will receive the accelerometer after the last revascularization. Patients who have their yearly routine checkup at our clinic will receive the accelerometer again after 1 year for another measuring period of 14 days (**Figure 1**). Patients who perform their yearly check-ups at an external cardiologist will receive the accelerometer for the follow-up measurement by mail. Detailed information concerning the occurrence of clinical outcomes (e.g., date and type of events) will be obtained from the CARDIOBASE database (NCT02241291), a prospective registry collecting all events adjudicated by an independent clinical events committee.

At each visit, all the assessments will be recorded on source documentation. A summary of the protocol activities is provided in **Figure 1**.

Measures

Physical activity monitoring

Tri-axial accelerometers (Axivity AX-3, Axivity Ltd., Newcastle, UK) will be worn continuously on the non-dominant wrist for 18 days. The devices will be programmed with the open-source software AX3 GUI V43 (16) to record tri-axial accelerations of ± 8 g at 50 Hz for 18 days starting on the evening of the day of hospital discharge. This period was chosen to achieve at least 14 days of physical activity data also from patients who are transferred to another hospital or home care before returning home. When patients return to the clinic for their follow-up visit after 1 year, they will receive again an accelerometer to be worn for 14 days. Patients completing their yearly follow-up visit with their resident cardiologist will be contacted by mail and if willing to wear the accelerometer again, they will receive it by mail with a prepaid returning envelope.

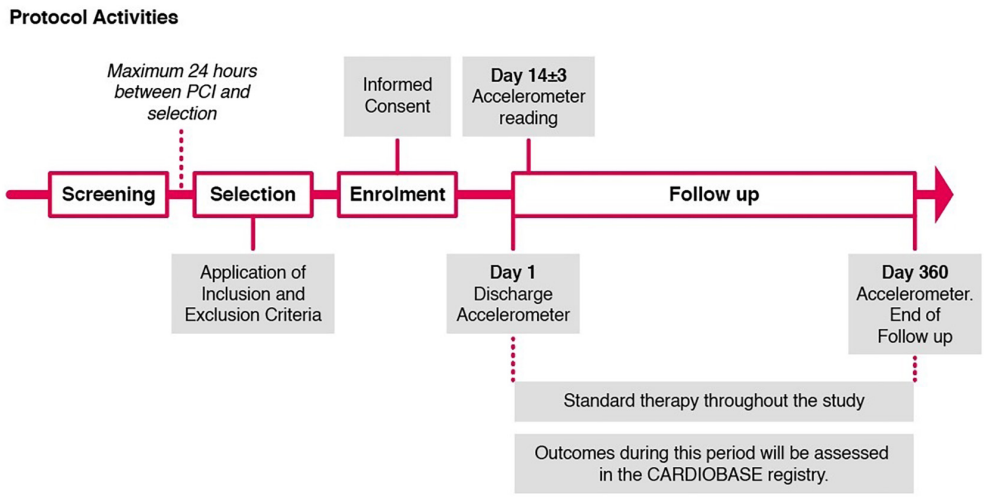

FIGURE 1
Protocol activities.

Data processing

Raw data will be downloaded as cwa files by AX3 GUI V43 and processed by a research-driven open-source R package named GGIR (version 2.4.0) (17, 18). Criteria for data inclusion for analysis is a minimum of 7 days of at least 12 h of daily wear time. The default acceleration metric of the package, which is the Euclidean norm (vector magnitude) minus one (ENMO), will be used for the calculations of the movement component of the raw acceleration data. It describes the conversion of the raw tri-axial acceleration data into an omnidirectional measure of body acceleration (19). The resulting ENMO values are expressed in gravity-based acceleration units (milligravity units [mg]) averaged over 5 s epochs [window sizes = c (5, 900, 3600)].

Physical activity levels

The following activity domains were pre-defined: (20) < 25 mg for inactivity, 25–99 mg for light physical activity [threshold.lig = c (25)] and ≥100 mg for moderate to vigorous physical activity (MVPA) [threshold.mod = c (100)]. Sleep will be identified by the longest daily time window with minimal acceleration and the least positional changes of the wrist (21, 22). Time spent at different PA levels will be accrued in 1 min bouts. During analysis, auto-calibration using local gravity as the reference will be conducted and non-wear time will be determined over a window size of 60 min with a 15-min sliding window [window sizes = c(5, 900, 3600)] (23, 24).

Steps

Whereas activity parameters will be derived directly from GGIR, steps will be determined by a Windowed Peak Detection open-source algorithm (Verisense_step_algorithm, last updated: 14.04.2021) based on the design of Gu et al. (25) and implemented for use in combination with the GGIR R package available on GitHub (26). The input parameters used for the step algorithm were validated in a study with 22 CVD patients during an outdoor exercise session of our CR program (27).

Cadence

Cadences for each minute will be calculated from the meta-data derived by the step algorithm, which includes the number of steps for each 5 s epoch. From this information, we will calculate the mean cadence over the whole 24 h cycle. Moreover, daily minutes with ≥100 steps/min and with 0 steps/min will be extracted (28). We will determine mean cadences for the most active 1, 30, and 60 min, as proposed by Tudor-Locke et al. (29).

Possible sources of bias

Patients cannot see activity or steps on the device, as there is no display on Axivity AX3. However, inherent to the observational design of the study, a selection bias may arise if patients with low PA levels refuse to wear the accelerometer. Information bias would be expected if patients do not wear the accelerometer on days when they move less, as they are told that they will get a personal data summary after the end of their wearing time. On the other hand, patients may make an extra effort to move more due to knowing that their data will be recorded and analyzed (Hawthorne effect).

Data analysis

Statistical analysis plan

All the statistical analyses will be performed in STATA 17IC and R. For all comparisons, a two-sided p-value < 0.05 will be considered statistically significant.

Descriptive statistics will be presented by relative frequencies for qualitative variables or by the mean and standard deviation (SD) or median and interquartile range (IQR), according to the normal distribution of quantitative variables. Unpaired T-tests, Chi-square tests and Mann–Whitney U tests will be used to present statistical differences in baseline characteristics according to the fulfilment of PA recommendations and the identified trajectories. If allowed by the data, we will perform logistic regression models to identify factors associated with short and long-term PA trajectories.

We will use group-based trajectory modeling (30) (GBTM) to identify distinctive clusters of individual PA trajectories and for profiling the characteristics of individuals within the trajectories. GBTM permits the analysis of the effect of time-stable covariates on the probability of group membership and the effect of time-dependent covariates on the trajectory itself (30).

We will test whether mean PA parameters of the whole observation period or trajectories could predict MACCE in addition to traditional risk factors. Furthermore, we will perform receiver operating characteristic (ROC) curves to identify a threshold of the most convenient time to start PA after coronary revascularization. Predictive values of daily steps during the first 2 weeks after hospital discharge will be quantified and tested by the increase in the area under the curve (AUC) of the ROC curve of a model consisting of traditional risk factors (age, sex, cardiovascular risk factors, cardiovascular history, and comorbidities) and time of starting PA after PCI.

We will also use Kaplan–Meier estimates to analyze the association of PA components including sedentary behavior, light, moderate, and high levels of activity, sleep, and the number of steps or step cadence with recurrent cardiovascular events after PCI. After inspection of Schoenfeld residuals to check the proportional hazards assumption, we will perform Cox regression models to compare rates of MACCE among trajectories. Furthermore, the models will be adjusted for age, sex, and clinically relevant variables, including acute vs. chronic CAD, staged PCI, and CR attendance, among others. Time-to-event will be censored at last patient contact for patients without MACCE. Multiple imputations will be performed in case of missing data.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

For all research activities, informed consent will be obtained from participants. Each participant will receive information about the objectives and the procedures of the study. After study completion, all the patients will receive their summary data. Only research team members will have access to data during the study, which will be stored in REDCap, and hosted on secure servers at Inselspital. All data will be anonymized, handled and stored in line with the national data protection laws in Switzerland (31). To protect the identity of participants, they will each be assigned a participant identification number (PIN). The list linking participants' names to their PIN will be stored separately and securely. Only the principal investigator will have access to that file. The project is approved by the cantonal ethics committee of Bern and is registered in ClinicalTrials (NCT04663373). The CARDIOBASE registry also complies with the Declaration of Helsinki and is approved by the ethics committee.

Author contributions

NG-J, AB, OF, PE, and MW designed the study. FC involved in the patient recruitment. SW, LR, and PE were involved in the data collection. NG-J and PE drafted the manuscript. All authors approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Effect of the full coverage policy of essential medicines on medication adherence: A quasi-experimental study in Taizhou, China

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Objective: Different forms of full coverage policy of essential medicines (FCPEMs) have been adopted worldwide to lower medication expenditure and improve adherence. This study aims to analyse the effect of FCPEMs on patients' medication adherence in Taizhou city, China.

Methods: This study was a quasi-experimental study and set treatment and control groups. We extracted Electronic Health Records (EHRs) for hypertension and diabetes 1 year before and after FCPEMs implementation and their medication adherence level assessed by physicians. We applied the propensity score matching (PSM) method to balance the bias between the two groups. Then, the descriptive analysis was used to compare the differences in the reported medication adherence. Using the Difference-In-Differences (DIDs) method, the fixed-effect model with the logistic regression was built to analyse the effects of FCPEMs.

Results: 225,081 eligible patients were identified from the original database. In the baseline year, FCPEM covered 39,251 patients. After PSM, 6,587 patients in the treatment group and 10,672 patients in the control group remained. We found that the proportion of patients with high adherence in the treatment group increased by 9.1% (60.8 to 69.9%, $P < 0.001$) and that in the control group increased by 2.6% (62.5 to 65.2%, $P < 0.001$). The regression results showed that FCPEMs significantly increased patients' medication adherence (OR = 2.546, $P < 0.001$).

Conclusion: FCPEMs significantly improved medication adherence. Socially disadvantaged individuals might benefit more from continuing FCPEM efforts. Expanding the coverage of FCPEMs to other medicines commonly used in patients with chronic diseases may be a promising strategy to manage chronic diseases and promote patient outcomes.

KEYWORDS

full coverage policy, essential medicines, medication adherence, free medicines, hypertension and diabetes, chronic diseases, China

Introduction

Medicine cost is one of the leading causes of suboptimal medication adherence and underutilization, aggravating disease burden, especially for chronic diseases. Reducing out-of-pocket expenses for evidence-based therapies proved an effective strategy for promoting rational use of medicines and lower rates of preventable complications (1–3). The full coverage policy was also known as "free," "full reimbursement," or "fee exemption" medicines policy. Full coverage policies of essential medicines (FCPEMs) were also put forward to improve the availability and affordability of essential medicines worldwide (4). According to the Pharmaceutical Country Profiles by the World Health Organization, all the 105 listed countries have made free medicines policies, and 54 provided full coverage for various medicines for essential medicine and 56 for chronic diseases (5).

Though FCPEMs implementation varied across countries and regions, many FCPEM programs prioritized vulnerable populations such as children and/or the elderly, patients from lower-income groups, and those with chronic diseases. For instance, Burkina Faso eliminates fees for healthcare utilization for children under five (6). Similar fee-exemption policies for children in primary care settings can be found in the US and Japan (7, 8). Brazilian National Health System provides free access to medicines for older adults in primary care (9), while Spain made prescription medicines free to elderly individuals (10). Other full coverage policies prioritized rural and low-income groups, as seen in France, Canada, and China (11–13). Many such programs also prioritized treatments for hypertension and diabetes due to their high incidence rates and serious consequences related to poor disease control (14–18). For example, the "Farmácia Popular" programme in Brazil made essential oral hypoglycaemic and antihypertensive medicines free to patients in 2011 (19). In the US, the Diabetes Health Plan reduced cost-sharing for metformin, statins, and ACE/ARBs (20). Research on medicine utilization showed that FCPEMs could increase the use of covered medicines and improve patients' overall adherence, though the extent of policy effect varied across studies (16, 19–21).

China bears a heavy burden from cardiovascular and kidney diseases due to complications of hypertension and diabetes (22, 23). Thus, prioritizing chronic disease control can have implications for the control of other diseases. To explore various strategies in chronic disease management, pilot FCPEMs have been launched in selected areas of 16 provinces in China by the end of 2020 (5, 12, 24, 25). However, studies examining the effect of policies on patients' medication adherence are limited. This study aims to analyse the effect of FCPEMs on patients' level of medication adherence with a longitudinal dataset in Taizhou, China, one of the first pilot areas, and to identify strategies to enhance adherence of patients with chronic diseases.

Methods

Study setting and policy introduction

Taizhou is a prefecture-level city with a total area of 10,050 km^2 in Zhejiang Province, located in the central area of the Yangtze River Delta in China. The city administers three urban districts (Jiaojiang, Huangyan, and Luqiao), three county-level cities (Linhai, Wenling, and Yuhuan) and three counties (Tianhai, Xianju, and Sanmen). In 2011, Taizhou had a population of 5.8 million, of which 9.1% were aged over 65 years, 19.3% were aged 45–64 years, and the per capita GDP was 7,287.4 dollars. There were 3,061 health institutions, 156 hospitals and health centers, 29,890 health professionals, 12,606 licensed physicians and 17,536 hospital beds (26).

To promote adherence to medicines and control of chronic disease, at the end of 2011, Taizhou city required all the nine districts and counties within its jurisdiction to establish a catalog between 2012 and 2013, specifying which hypertension and diabetes medicines are listed in China's National Essential Medicines List (version 2012) were to reimburse in full (27, 28). In June 2012, Huangyan was the first district in Taizhou to announce its reimbursement list of hypoglycaemic (metformin hydrochloride and glipizide tablets) and antihypertensive medicines (captopril and indapamide tablets), and all districts implemented their respective FCPEM policies in October 2013. All patients living in Taizhou could access to medicines listed in this catalog without any costs, including drug, prescription and related medical costs, at any primary care or designated facilities. As part of the basic public health services, from the new healthcare reform in 2009, China has established health records and provided free chronic disease management services for hypertension and diabetes (29, 30). According to the FCPEMs of Taizhou, physicians at primary care and designated facilities were responsible for maintaining health records of patients, providing regular follow-ups, recording and reporting the medicines' clinical benefits, evaluating appropriateness for the patient and adjusting the medicine plan, such as quitting free medicines if clinical outcomes were poor. All patients' prescriptions benefiting from the FCPEMs were integrated into their Electronic Health Records (EHRs), which gather local patients' health records, including demographics, diagnosis and disease profile, medicine use, and health behaviors.

Study design

This study was a quasi-experimental study, which set treatment and control groups and used the longitudinal EHRs data to examine the effect of FCPEMs policy on patients' medication adherence. We controlled for confounding factors

between two groups using the difference-in-differences (DIDs) method (31) and analyzed the difference in changes in medication adherence between the two groups 1 year before and after the policy implementation. Huangyan district was identified as the treatment group as it was the first to implement the FCPEMs in Taizhou. Linhai and Wenling were regarded as the control group. We applied the propensity score matching (PSM) using nearest neighborhood matching to eliminate possible influences of substantial baseline differences between groups, ensuring a more rational interpretation of the causal effect. We applied a caliper of 10^{-6} to reduce the matching tolerance and allowed equally qualified objects to retain in this step.

We conducted analysis on both the whole and the matched samples to ensure the stability of the results.

Data source and study population

We extracted EHR data from Taizhou's database for chronic disease management. Due to a system upgrade, data from six districts were inaccessible and thus excluded from our study. Therefore, only Linhai and Wenling were altogether taken as the control group. We defined records collected from Huangyan, Wenling and Linhai between June 2011 and June 2012 as the baseline data. As Wenling and Linhai announced the FCPEMs in February and October 2013, we defined follow-up data as records from June 2012 to June 2013 in Huangyan and Linhai, and from June 2012 to February 2013 in Wenling. We subsequently established a 2-year cohort dataset. Figure 1 illustrates details of the study timeline.

Outcome measure

According to the requirements and regulations of the Chronic Disease Management Services of China, family physicians should administer follow-up surveys regularly and file follow-up records into EHRs. The EHRs system categorizes adherence indicators into "regular medicine use," "interrupted medicine use," or "taking no medicine" at each follow-up. In this analysis, "regular medicine use" was identified as high adherence (=1) while "irregular medicine use" and "taking no medicine" were regarded as poor adherence (=0).

Besides the primary variable of concern, categorical variables, including the patient's characteristics, socioeconomic status, and health behaviors, were identified as controls and used for PSM (Table 1). These included the patient's age, gender, insurance scheme, annual average BMI index, marital status, monthly household income per person, employment status, educational attainment, smoking and drinking habit, and hypertension and diabetes history.

Statistical approaches

The study conducted a descriptive analysis to indicate the impacts of the FCPEMs on medication adherence, with Student's T Test for continuous variables and Chi-square Test for categorical variables. We constructed a fixed-effect model with logistic regression would be constructed to ascertain the statistical significance of the findings, ensuring the scientific and rigorous interpretation of our study results. The DIDs method is incorporated into the fixed-effect model to control for heterogeneity. The analytic model was constructed as:

$$logit\ Y_{it} = \beta_0 + \beta_1\ Group_i \times Time_t + \beta_2\ Group_i + \beta_3\ Time_t + \beta\ X_{it} + \varepsilon_{it} \quad (1)$$

Where Y_{it} denoted medicine adherence of every individual at different times, *Group* represented the individual's participation category (=1 if in the treatment group, = 0 if in the control group), *Time* indicated the stage of policy implementation (=1 if after policy implementation, =0 if prior to implementation), β_0 was the regression intercept, and ε_{it} denoted an idiosyncratic error that changed across individuals and time. X_{it} captured other individual and household characteristics for control. The coefficient of interest β_1 gave the estimate of the average treatment effect of FCPEMs on medication adherence. The coefficients were interpreted in terms of odds ratio (OR).

All analyses were programmed in STATA 14.0.

Results

Characteristics of study population

225,081 patients and their respective records were included in the baseline year. Among them, 39,251 patients were covered by FCPEMs. Table 1 showed that all variables of concern differed significantly at the 0.001 significance level between the treatment and control groups of the original cohort. After PSM, 6,587 and 10,672 patients remained in the treatment and control groups, respectively. Baseline differences in most variables were eliminated at the 0.05 level, except for medication adherence ($P = 0.043$), residence ($P = 0.005$), and employment status ($P = 0.006$).

Description of changes in medication adherence

As indicated in Table 2, the sample population increased from 225,081 to 267,854 patients during the study period, while the cohort size after PSM slightly decreased from 17,259 to

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TABLE 1 Characteristics of study population before and after PSM.

Variables	Description	Before PSM			After PSM		
		Treatment ($n = 39,251$)	Control ($n = 185,830$)	*P*	Treatment ($n = 6,587$)	Control ($n = 10,672$)	*P*
Medication adherence	High adherence	48.5%	51.1%	0.000	62.5%	60.8%	0.043
	Poor adherence	51.5%	48.9%		37.5%	39.2%	
Gender	Female	62.7%	59.6%	0.000	70.4%	70.1%	0.703
	Male	37.3%	40.4%		29.6%	29.9%	
Age, years	0–64	51.0%	49.1%	0.000	54.3%	55.0%	0.473
	≥65	49.0%	50.9%		45.7%	45.0%	
Household monthly income	≤500	11.5%	8.9%	0.000	8.7%	7.8%	0.586
per person, CNY[a]	500–3,000	51.0%	38.9%		47.5%	47.9%	
	≥3,000	37.5%	52.2%		43.8%	44.3%	
Residential terrain	Plain area	80.4%	73.2%	0.000	90.1%	88.6%	0.005
	Mountainous area	19.6%	26.8%		9.9%	11.4%	
Marital status	Married[b]	83.1%	80.8%	0.000	85.2%	85.9%	0.265
	Single[c]	16.9%	19.2%		14.8%	14.1%	
Employment status	Employed	5.9%	17.0%	0.000	3.5%	2.6%	0.006
	Unemployed[d]	94.1%	83.0%		96.5%	97.4%	
Education attainment	Illiterate	34.5%	45.8%	0.000	40.1%	39.8%	0.530
	Primary school	45.2%	39.9%		47.0%	47.1%	
	Secondary school	17.0%	11.9%		11.8%	11.8%	
	High school and above	3.3%	2.4%		1.2%	1.3%	
Insurance	None	2.5%	14.2%	0.000	2.0%	2.0%	0.203
	URRBMI[e]	93.1%	84.3%		97.5%	97.6%	
	UEBMI/CMI[f]	4.4%	1.5%		0.5%	0.4%	
BMI, kg/m^2	Average BMI	23.1	23.4	0.000	23.1	23.0	0.732
Smoking	Yes	18.5%	2.6%	0.000	3.2%	2.7%	0.078
	No	81.5%	97.4%		96.8%	97.3%	
Drinking	Yes	12.3%	1.6%	0.000	1.9%	1.9%	0.898
	No	87.7%	98.4%		98.1%	98.1%	
Disease	Hypertension	81.6%	83.9%	0.000	74.4%	74.4%	1.000
	Diabetes	18.4%	16.1%	0.000	25.6%	25.6%	

[a]CNY, Chinese yuan. [b]Married including married and remarried. [c]Single including unmarried, divorced, and widowed. [d]Unemployed including unemployed and rural residents. [e]URRBMI, Urban-rural resident basic medical insurance. [f]UEBMI/CMI, Urban employee basic medical insurance or/and commercial medical insurance.

TABLE 2 The proportion of patients with high adherence before and after FCPEMs.

Group	Before PSM			After PSM		
	Before FCPEMs	After FCPEMs	Diff	Before FCPEMs	After FCPEMs	Diff
Control group	51.1%	56.4%	5.3%***	62.5%	65.2%	2.6%***
	($n = 185,830$)	($n = 216,735$)		($n = 10,672$)	($n = 10,412$)	
Treatment group	48.5%	67.0%	18.5%***	60.8%	69.9%	9.1%***
	($n = 39,251$)	($n = 51,119$)		($n = 6,587$)	($n = 6,430$)	
ΔDiff			13.2%			6.5%

***$P < 0.001$.

FIGURE 1
Study timeline. Wenling implemented the FCPEMs in February 2013. Linhai launched its respective policy in October 2013, which is beyond the study period.

16,842 patients. The proportion of patients with high adherence without matching increased by 5.3% (51.1–56.4%, $P < 0.001$) among the control group and 18.5% (48.5–67.0%, $P < 0.001$) among the treatment group. After matching, the proportion of patients with high adherence in the control group increased by 2.6% (62.5–65.2%, $P < 0.001$) and that in the treatment group increased by 9.1% (60.8–69.9%, $P = P < 0.001$). The results showed that FCPEMs could promote medication adherence.

Regression analysis on the effects of FCPEMs

As the fixed-effect model omitted all time-invariant covariates, only Group × Time (policy indicator), Time, Age, BMI, Smoking and Drinking were retained in the results. Table 3 shows the results of the fixed-effect regression analysis before and after PSM. FCPEMs had a significant positive impact on patients' medication adherence in both the original sample (OR = 2.825, $P < 0.001$) and the sample after PSM (OR = 2.546, $P < 0.001$). That means the treatment group had 2.825 times more likely to be high adherence than the control group in the original sample and 2.546 times in the sample after PSM. Patients' medication adherence experienced a natural increase with the progression of time in samples without PSM (OR = 2.285, $P < 0.001$) and with PSM (OR = 1.647, $P < 0.001$). Moreover, results from the unmatched sample indicated that the patient's BMI level had a significant positive association with adherence (OR = 1.033, $P = 0.009$). Other factors present no statistically significant effects on the outcome.

Discussion

This study found that FCPEMs could significantly promote medication adherence based on patient-level data. The proportion of patients with high level of medication adherence increased by 13.2% (18.5–5.3%) in the unmatched population and by 6.5% (9.1–2.6%) after matching. The fixed-effect model further suggested that the policy effect was statistically significant, which aligns with results from previous literature (16–21, 32). Yet, FCPEMs in Taizhou covered only four hypertensive and diabetic medicines, which might not meet the complex and diverse needs of patients (2). Future policy design should target medication adherence and consider expanding the success of pilot FCPEMs interventions across the system with considerations of treatment algorithms. For example, Brazilian 'Farmácia Popular' offered 17 kinds of hypertensive and diabetic medicines for free and achieved remarkable adherence improvement (19) while the US Diabetes Health Plan covering only three medicines only showed a modest adherence rise (20).

Furthermore, many policy beneficiaries in our cohort sample were vulnerable populations, which have implications for studies in disadvantaged settings. Studies have revealed that socially disadvantaged groups demonstrated a lower adherence to medicine due to costs (5, 12, 25). Suboptimal medication adherence further compromises patient health due to increased risk of disease complications, aggravates the burden of disease control, and increases overall healthcare costs. In our study, 19.6% of the treatment group and 26.8% of the control group were residents in remote mountainous areas and unemployment and illiteracy rates were high, with 94% of the treatment group unemployed. 62.4% of the entire sample cohort had a households' monthly income per diem of <3,000 yuan (475.25 USD) and 11.5% had that of even <500 yuan (79.21 USD), which was in stark contrast to Taizhou's average monthly per capita income of 3917.25 yuan (620.55 USD) in 2012. 93.1% of the patients benefiting from FCPEM were enrolled in the URRBMI scheme, which had poor coverage for treatments of chronic diseases. URRBMI beneficiaries with chronic diseases thus might experience lower access to medicines needed and compromised health (33, 34). FCPEMs can be an effective strategy to promote equitable access to medicines, promote

TABLE 3 Fixed-effect regression analysis of the effect of FCPEMs on medication adherence.

Variables	Before PSM		After PSM	
	OR value (95% CI)[a]	*P*	OR value (95% CI)	*P*
Group × Time-FCPEMs	2.825 (2.567–3.099)	0.000	2.546 (2.028–3.197)	0.000
Time, year	2.285 (2.186–2.388)	0.000	1.647 (1.404–1.933)	0.000
Age ≥ 65	1.061 (0.810–1.389)	0.667	1.900 (0.601–6.006)	0.274
BMI, kg/m^2	1.033 (1.008–1.059)	0.009	0.998 (0.920–1.083)	0.962
Smoking-Yes	0.864 (0.739–1.010)	0.066	1.434 (0.682–3.014)	0.342
Drinking-Yes	0.869 (0.712–1.060)	0.166	0.673 (0.301–1.505)	0.335

[a]OR, odds ratio; CI, confidence interval.

patient health, and safeguard vulnerable populations from financial burdens due to medical costs. The Chinese Bureau of Statistics stated that by 2020, 551.62 million population would reside in rural areas of China, and more than 190.45 million people would be employed in the primary industry with an average monthly income of <3,000 CNY (434.78 USD). The World Bank stated that 8.6% of the world population lived under extreme poverty (<59 USD per month), and 1.3 billion people lived in households with multiple layers of deprivations (35). Our findings add to the case for prioritizing the implementation of FCPEMs to improve adherence and alleviate economic and disease burdens.

Our study, however, is subject to several limitations. First, though randomized controlled study design remains the golden standard in examining the effect of the interventions, the assignment to FCPEM in this study was not rigorously randomized. We controlled for the bias with PSM and the fixed-effect model constructed with the DIDs method and subsequently formed a quasi-randomized controlled study design. Still, there were likely other influential factors of medication beyond our scope (36, 37). Second, medication adherence in filed records was assessed by the patient's self-reported adherence. This might have introduced biases. Third, though we aimed to minimize the impact of sample selection on the study outcome by improving the sample representativeness with more generalized policy beneficiaries in this study, whether our study findings are generalisable to other diseases awaits further justifications.

Conclusion

This study found that FCPEMs is an effective strategy to improve adherence to medicines for chronic diseases, with PSM controlling for baseline biases and the fixed-effect model eliminating time-invariant unobservable factors. For patients with hypertension and diabetes, FCPEMs in Taizhou resulted in a substantial increase in the level of adherence to antidiabetic and antihypertensive medicines. Meanwhile, as our treatment group was mostly vulnerable populations, FCPEMs could be a promising strategy to protect socially disadvantaged groups. Policymakers should consider reducing or removing cost-sharing for essential medicines for chronic diseases.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: The data used in the study are non-public electronic health records belonging to the health department of Taizhou city, Zhejiang. The data contains patients' personal information, so other researchers need permission from Taizhou city's health department to access the data. Some detailed statistical data underlying this article will be shared on reasonable request to the corresponding author. Requests to access these datasets should be directed to guanxiaodong@pku.edu.cn.

Ethics statement

The studies involving human participants were reviewed and approved by Peking University Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

ZG, XG, and LS conceptualized and designed the study and contributed to data collection. ZG and LZ participated in data analysis. ZG, ZH, and XG conducted the final analyses and contributed to the interpretation of the results. ZG, ZH, XG, and LS drafted the initial manuscript. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer DZ declared a shared affiliation with the authors to the handling editor at the time of the review.

Publisher's note

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Association between level of depression and coronary heart disease, stroke risk and all-cause and cardiovascular mortality: Data from the 2005–2018 National Health and Nutrition Examination Survey

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Research on the association between level of depression and coronary heart disease (CHD), stroke risk, and all-cause and cardiovascular mortality is lacking in large-scale or population-based studies incorporating cardiovascular disease (CVD) endpoints. We aim to assess the relationship between the level of a person's depression and their risk of CHD, stroke, and all-cause and cardiovascular mortality. Utilizing data from the United States National Health and Nutrition Examination Survey (NHANES), multicycle cross-sectional design and mortality linkage studies were conducted. The study sample included 30918 participants aged 20–85 years old during the 2005–2018 period. Depression was assessed using the nine-item Patient Health Questionnaire (PHQ-9), with scores of 5, 10, 15, and 20 being the cut-off points for mild, moderate, moderately severe, and severe depression, respectively. A series of weighted logistic regression analyses and Cox proportional hazards models were utilized to examine the relationship between the level of depression with the risk of CHD, stroke, all-cause, and cardiovascular mortality. Trend analyses were conducted by entering the level of depression as a continuous variable and rerunning the corresponding regression models. Weighted logistic regression models consistently indicated a statistically significant association between the level of depression and increased risk of CHD and stroke, and those linear trend tests were statistically significant (P for trend < 0.001). Furthermore, weighted Cox regression analyses consistently indicated that participants who had a more severe degree of depression were at a higher risk of all-cause death, and trend analyses suggested similar results (P for trend < 0.001). Another weighted Cox regression analysis also consistently

indicated that except for severe depression, the hazard of cardiovascular death was increased with each additional level increase of depression. Our study confirmed that the level of depression was strongly associated with CHD, stroke, and all-cause and cardiovascular mortality, even after accounting for other factors that could impact risk, including variables of age, gender, ethnicity, income, education, body mass index (BMI), marital, and smoking status.

KEYWORDS

coronary heart disease, stroke, depression, NHANES, PHQ-9, mortality

Introduction

According to the World Health Organization (WHO), depression was ranked as the single largest contributor to global disability and non-fatal health loss; current estimates are that approximately 4.4% of the population worldwide, that is to say, about 264 million people, suffers from depressive disorder—a chronic and recurrent condition—imposing a significant extra burden on public health (1).

Cardiovascular diseases often co-occur with depression (2–4), and the two are projected to be the top two leading contributors to the global disease burden by 2030 (5). In particular, CHD was also the main cause of global morbidity and mortality, being responsible for roughly one-third of all deaths for people aged over 35 years worldwide (6).

Cardiovascular diseases were influenced by and associated with a variety of aspects of health and wellbeing, especially mental health. A recent study has reported that depression symptom history may be a predictor or marker of cardiometabolic risk over decades (7). Thus, by understanding the impact of the link, doctors can improve a patient's overall health by addressing both mental health and heart disease together. Several prior research studies have examined the relationship between depression and CVDs from two perspectives: depression's impact on CVDs and depression as a risk factor for poor prognosis among patients with CVDs (3, 8–12).

To date, studies have demonstrated that depression is a leading contributor to an elevated risk of morbidity and mortality for CVDs, such as CHD and stroke (9, 13–15). However, until recently, research on the association between the level of depression and CHD, stroke risk, and all-cause and cardiovascular mortality are nevertheless lacking in large-scale or population-based studies incorporating CVD endpoints.

We hypothesized that the severity of a person's depression may elevate their risk of CHD, stroke, and mortality. Thus, to test our hypothesis, multicycle cross-sectional design and mortality linkage studies were conducted to assess the relationship between the level of depression and CHD, stroke risk, and mortality, utilizing data from the NHANES.

Materials and methods

Database

Data were collected from the multiple cycles of the United States cross-sectional Continuous NHANES from 2005 to 2018. Moreover, the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention (CDC) (16) provided NHANES public-use linked mortality follow-up files until 31 December 2019, and it has linked several population surveys to death certificate records from the National Death Index (NDI) (17).

The NHANES uses a complex, stratified multistage, probability cluster design to produce a nationally representative survey of the health and nutritional status of the non-institutionalized civilian population in the United States, with full details provided in the NHANES survey methods and analytic guidelines (18). Information on nutritional health and the status of non-institutionalized civilians of the United States population is gathered through a series of home interviews, examinations, and laboratory measurements.

Study population

The original sample is comprised of seven successive cycles collected in 2-year increments from 2005 to 2018 of the continuous NHANES. The inclusion criteria were as follows: participants from the 2005 to 2018 annual NHANES cycles aged 20–85 years at the time when NHANES data were collected where there was accessible data on CHD and stroke status and where the participant depression questionnaire data were included in the analysis.

Data collection

This is a prospective cohort study. Information on demographics, comorbidities, and body measurements was collected. Demographic and comorbidities data were

recorded in a home interview by household questionnaire. Standardized body measurements (e.g., BMI) and the questions from the PHQ-9 were provided by trained field health technicians for all examinees in the mobile examination center (MEC).

Laboratory tests

On the Modular Chemistry side of the DxC800, the concentration of blood glucose and 2-h oral glucose tolerance test (OGTT) blood glucose in biological fluids were determined by the oxygen rate method by employing a Beckman Oxygen electrode (glucose oxidase method). A precise volume of sample was introduced in a reaction cup containing an electrode that responds to oxygen concentrations. Electronic circuits determined the rate of oxygen consumption, which was directly proportional to the concentration of glucose in the sample.

Hemoglobin A1c (HbA1c) was measured in whole blood at the University of Missouri-Columbia using the Primus CLC 330 and Primus CLC 385 instruments (Primus Corporation, Kansas City, Missouri, USA) for the high-performance chromatography.

These laboratory procedure manuals were available on the NHANES website (18).

Primary study variables

Assessment of CHD and stroke

Participants who answered "yes" to the question "has a doctor or other health professional ever told you that you had CHD/stroke?" on the medical conditions section of the household questionnaire through home interview were considered to have CHD/stroke.

Independent variable

Assessment of depressive symptoms

The PHQ-9 represents a nine-item instrument for screening depression. And the instrument incorporates the Diagnostic and Statistical Manual (DSM)-IV depression diagnostic criteria (19).

Depression was measured using PHQ-9, a continuum scale of severity from minimal to severe, with scores of 5, 10, 15, and 20 being the cut-off points for mild, moderate, moderately severe, and severe depression, respectively. Those with PHQ-9 total scores $\geq$10 were considered as having clinically relevant depression (19, 20), which corresponded with moderate to severe depression symptoms.

Covariates and confounders

A number of potential confounding variables were taken into consideration. Age was split into groups: 20–30, 31–40, 41–50, 51–60, 61–70, 71–80, and 81–85 years old. Gender was divided into male and female participants. Ethnicity was classified as White, Black, Mexican, and other races. The classification of marital status included married, living with partner, separated, divorced, widowed, and never married. Educational level was categorized as college graduate or above, some college or AA degree, high school graduate, 9–11th grade, and less than ninth grade.

The poverty income ratio (PIR) was used to measure income, which was calculated by dividing family income by the poverty guidelines, specific to family size, as well as the appropriate year and state. The values were not computed if the income screener information [income questionnaire (INQ) 220: $<$ \$20,000 or $\geq$ \$20,000] was the only family income information reported. If family income was reported as a range value, the midpoint of the range was used to compute the variable. Values at or above 5.00 were coded as 5.00 or more due to disclosure concerns. There were five distinct categories of PIR: poor (i.e., $<$1.0), nearly poor (i.e., 1.0–1.9), middle income (i.e., 2.0–3.9), high income (i.e., $\geq$4.0), and unknown (not acquired).

Smoking status was categorized as former, current, or never. BMI was divided into four categories according to the CDC classification for adults 20 years old and older: low ($<$18.5 kg/m^2), normal (18.5–25 kg/m^2), and overweight ($\geq$25 kg/m^2) (21).

History of CVDs, cancer, or malignancy

Information on past medical history was self-reported by participants. Regarding the question "Have you ever been told by a doctor or health professional that you had CHD/angina, also called angina pectoris/heart attack (also called myocardial infarction)/stroke/congestive heart failure (CHF)/cancer or a malignancy of any kind?", persons who answered "yes" were perceived as having a history of CVDs, cancer, or malignancy.

Other comorbid conditions

Information on comorbidities was self-reported by participants. Regarding the question "Have you ever been told by a doctor or health professional that you have …?", persons who answered "yes" were perceived as having the following comorbidities: hypertension, CHF, angina/angina pectoris, arthritis, and hyperlipidemia.

Other than that, Parkinson's disease was diagnosed by taking anti-Parkinson agents, and the diagnostic criteria for diabetes

were as follows: doctor-diagnosed diabetes; glycohemoglobin HbA1c (%) > 6.5; random blood glucose (mmol/l) ≥ 11.1; 2-h OGTT blood glucose (mmol/l) ≥ 11.1; and use of diabetes medication or insulin.

Follow-up

The period of follow-up was from the date of the interview to the last follow-up time, 31 December 2019, or the date of death. Causes of death for these included participants were documented in death certificate records from the NDI.

Outcomes

The endpoints for this study were all-cause and cardiovascular mortality. All-cause mortality encompassed all known and unknown causes, whereas cardiovascular mortality was defined using the International Classification of Diseases coding (ICD-9 and ICD-10), including the death from diseases of the heart (I00–I09, I11, I13, I20–I51) and cerebrovascular diseases (I60–I69).

Statistical analysis

R software (version 4.1.2, https://www.R-project.org) was utilized to conduct statistical analysis.

In the original NHANES surveys, responses coded as "missing," "refused," or "do not know" were treated as missing. Participants with missing data in one of the primary study covariates mentioned above or without mortality information were not included for further analysis.

Weighted proportions of descriptive statistics were employed to summarize the characteristics of the study sample; the design-based χ^2-test was used to examine the associations of categorical variables with depression.

A subgroup analysis was conducted to investigate whether the association between CHD, stroke, and depression varied across different subgroups of study covariates and comorbid conditions, separately. We examined the interaction effects of CHD and stroke with PHQ-9 score in several participant subgroups (gender, age grouping, ethnicity, marital status, educational level, PIR grouping, smoking status, BMI grouping), and the *P*-value for interaction was determined by the Wald test.

After univariate analysis and referring to previous studies and related literature (22–26), weighted logistic regression analyses were conducted to assess the association of CHD and stroke with the severity of depression in three models to control for potential confounding variables. Model 1 was the unadjusted model; model 2 included the level of depression, age, gender, and ethnicity; and model 3 adjusted for age, gender, ethnicity, marital status, family PIR, education, smoking status, and BMI. Crude and adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) between CHD, stroke, and depression severity were presented.

Likewise, after excluding the participants with CVDs, cancer, or malignancy at baseline, a series of weighted Cox regression analyses was performed to estimate the relationships between the level of depression and risk of having all-cause and cardiovascular mortality, respectively, after adjusting for potential confounders in three models. Model 1 only included the level of depression, and no covariates were adjusted. Model 2 adjusted for age, gender, and ethnicity. Model 3 was further adjusted for marital status, family PIR, education, smoking status, and BMI. Crude and adjusted hazard ratios (HR) and their 95% CI between the level of depression and outcomes were presented.

We determined the first level of depression—no/minimal depression, which corresponded with the PHQ-9 scores ranging from 0 to 5, as the reference group. Trend analyses were conducted by entering the level of depression as a continuous variable and rerunning the corresponding regression models.

In all analyses, the complexity of the sampling design was taken into consideration by specifying primary sampling units (PSUs), strata, and weights using the R package "survey" (version 4.1-1). A good rule of thumb is to use "the least common denominator" where the variable of interest that was collected on the smallest number of respondents is the "least common denominator". That is to say, we must use the weight of the smallest subpopulation that includes all the variables we want to include in our analysis. Reviewing the documentation file for each component included in our analysis, we used MEC exam weights to generate nationally representative estimates (27–29). To account for multiple testing, the method of Benjamini–Hochberg was used to correct the false discovery rate (FDR), and a two-sided FDR-adjusted *P*-value (i.e., q-value) <0.05, corresponding to an FDR of 5%, was deemed statistically significant for testing the study's hypotheses.

Results

Sample characteristics

A total of 34,079 NHANES participants aged 20–85 years old during the 2005–2018 period were interviewed. The 3,161 (9.28%) participants with missing data, and the final analysis unweighted sample consisted of 30,918 participants, representing 189.00 million non-institutionalized residents of the United States. Of those, 2,700 people (weighted proportion of 7.59%) reported symptoms of depression from moderate to severe, 1,231 people (weighted proportion of 3.39%) reported CHD, and 1,149 people (weighted proportion of 2.80%) reported stroke. These translated to

TABLE 1 Baseline characteristics of study participants[a].

Characteristic	Total	No depression (PHQ-9 < 10)	Depression (PHQ-9 ≥ 10)	Missing data, number (%)	Raw *P* value	q value
Gender (%)				0 (0.00)	< 0.0001	< 0.0001
Male	49.37 (47.20, 51.54)	50.29 (49.70, 50.89)	35.26 (32.72, 37.80)			
Female	50.63 (48.37, 52.89)	49.71 (49.11, 50.30)	64.74 (62.20, 67.28)			
Age (%)				0 (0.00)	< 0.0001	< 0.0001
[20, 30]	19.88 (18.74, 21.01)	19.95 (18.93, 20.96)	18.78 (16.18, 21.37)			
[31, 40]	17.55 (16.64, 18.47)	17.56 (16.84, 18.29)	17.43 (15.19, 19.67)			
[41, 50]	19.37 (18.15, 20.60)	19.23 (18.43, 20.03)	21.61 (19.29, 23.93)			
[51, 60]	18.76 (17.57, 19.95)	18.57 (17.78, 19.36)	21.68 (19.36, 24.00)			
[61, 70]	13.69 (12.75, 14.63)	13.73 (13.04, 14.42)	13.09 (11.16, 15.01)			
[71, 80]	10.34 (9.63, 11.05)	10.54 (9.95, 11.12)	7.30 (5.92, 8.68)			
[81, 85]	0.41 (0.30, 0.51)	0.43 (0.32, 0.54)	0.12 (0.00, 0.26)			
Ethnicity (%)				0 (0.00)	< 0.0001	< 0.0001
White	68.72 (63.66, 73.78)	69.05 (66.61, 71.49)	63.74 (60.00, 67.49)			
Black	10.43 (9.37, 11.49)	10.23 (8.96, 11.51)	13.39 (11.47, 15.30)			
Mexican	8.35 (7.15, 9.55)	8.38 (7.08, 9.67)	7.92 (6.05, 9.80)			
Other	12.50 (11.55, 13.45)	12.34 (11.24, 13.44)	14.95 (12.75, 17.15)			
Marital status (%)				19 (0.06)	< 0.0001	< 0.0001
Married	55.85 (52.66, 59.05)	57.11 (55.81, 58.40)	36.65 (33.72, 39.59)			
Living with partner	8.20 (7.57, 8.82)	8.01 (7.47, 8.55)	11.06 (9.37, 12.75)			
Separated	2.37 (2.15, 2.59)	2.13 (1.91, 2.36)	5.96 (4.87, 7.05)			
Divorced	10.41 (9.75, 11.06)	9.90 (9.41, 10.40)	18.06 (16.25, 19.88)			
Widowed	5.52 (5.13, 5.91)	5.40 (5.08, 5.73)	7.34 (5.96, 8.71)			
Never married	17.66 (16.68, 18.63)	17.44 (16.35, 18.53)	20.93 (18.79, 23.07)			
Educational level (%)				26 (0.08)	< 0.0001	< 0.0001
College graduate or above	29.77 (27.44, 32.10)	30.85 (29.02, 32.69)	13.21 (10.83, 15.59)			
Some college or AA degree	31.79 (30.24, 33.35)	31.68 (30.66, 32.70)	33.47 (30.66, 36.28)			
High school graduate	23.27 (21.79, 24.75)	23.00 (22.03, 23.97)	27.42 (24.90, 29.95)			
9–11th grade	10.18 (9.32, 11.04)	9.72 (8.93, 10.50)	17.31 (15.28, 19.34)			
<9th Grade	4.98 (4.50, 5.47)	4.75 (4.27, 5.22)	8.59 (7.20, 9.97)			
Poverty income ratio (%)				0 (0.00)	< 0.0001	< 0.0001
High income	35.17 (32.57, 37.77)	36.35 (34.60, 38.11)	17.12 (14.45, 19.78)			
Middle income	27.15 (25.48, 28.82)	27.52 (26.41, 28.63)	21.50 (19.06, 23.93)			
Nearly poor	18.76 (17.65, 19.87)	18.22 (17.30, 19.14)	27.05 (24.38, 29.73)			
Poor	12.52 (11.69, 13.35)	11.53 (10.71, 12.35)	27.56 (24.89, 30.23)			
Unknown	6.40 (5.84, 6.97)	6.38 (5.84, 6.92)	6.77 (5.41, 8.14)			
Smoking status (%)				17 (0.05)	< 0.0001	< 0.0001
Never	54.65 (52.29, 57.01)	55.74 (54.62, 56.86)	37.95 (34.77, 41.13)			
Former	25.16 (23.54, 26.77)	25.38 (24.49, 26.26)	21.76 (19.22, 24.31)			
Current	20.20 (19.02, 21.37)	18.88 (18.04, 19.72)	40.29 (37.21, 43.36)			
Body mass index (%)				335 (0.98)	0.003	0.003
Normal	27.98 (26.50, 29.46)	28.28 (27.33, 29.24)	23.30 (20.54, 26.06)			
Overweight	70.54 (67.30, 73.78)	70.26 (69.24, 71.28)	74.77 (72.03, 77.51)			
Low	1.48 (1.30, 1.67)	1.46 (1.28, 1.63)	1.93 (0.91, 2.95)			
CHD (%)				0 (0.00)	< 0.001	0.005
No	96.61 (92.48, 100.74)	96.72 (96.40, 97.04)	94.91 (93.63, 96.18)			
Yes	3.39 (3.03, 3.75)	3.28 (2.96, 3.60)	5.09 (3.82, 6.37)			

(Continued)

TABLE 1 (Continued)

Characteristic	Total	No depression (PHQ-9 < 10)	Depression (PHQ-9 ≥ 10)	Missing data, number (%)	Raw *P* value	q value
Hypertension (%)				0 (0.00)	< 0.0001	< 0.0001
No	61.95 (59.08, 64.82)	62.62 (61.57, 63.67)	51.74 (49.22, 54.26)			
Yes	38.05 (36.15, 39.95)	37.38 (36.33, 38.43)	48.26 (45.74, 50.78)			
CHF (%)				55 (0.16)	< 0.0001	< 0.0001
No	97.81 (93.62, 102.00)	98.01 (97.81, 98.21)	94.69 (93.65, 95.72)			
Yes	2.19 (1.97, 2.42)	1.99 (1.79, 2.19)	5.31 (4.28, 6.35)			
Angina (%)				71 (0.21)	< 0.0001	< 0.0001
No	97.84 (93.66, 102.02)	98.02 (97.82, 98.23)	95.05 (93.86, 96.24)			
Yes	2.16 (1.93, 2.39)	1.98 (1.77, 2.18)	4.95 (3.76, 6.14)			
Heart attack (%)				35 (0.10)	< 0.0001	< 0.0001
No	96.71 (92.59, 100.84)	96.88 (96.61, 97.16)	94.09 (92.95, 95.23)			
Yes	3.29 (2.97, 3.60)	3.12 (2.84, 3.39)	5.91 (4.77, 7.05)			
Stroke (%)				36 (0.11)	< 0.0001	< 0.0001
No	97.20 (93.04, 101.37)	97.50 (97.28, 97.71)	92.76 (91.47, 94.04)			
Yes	2.80 (2.55, 3.04)	2.50 (2.29, 2.72)	7.24 (5.96, 8.53)			
Arthritis (%)				58 (0.17)	< 0.0001	< 0.0001
No	73.88 (70.69, 77.07)	75.02 (74.09, 75.95)	56.42 (53.80, 59.05)			
Yes	26.12 (24.57, 27.67)	24.98 (24.05, 25.91)	43.58 (40.95, 46.20)	1686 (4.95)		
CKD (%)					< 0.001	0.0008
No	85.93 (82.10, 89.77)	86.12 (85.50, 86.73)	83.14 (81.36, 84.93)			
Yes	14.07 (13.29, 14.84)	13.88 (13.27, 14.50)	16.86 (15.07, 18.64)			
CKD prognosis (%)				2001 (5.87)	< 0.0001	0.0005
Low risk	85.93 (82.10, 89.77)	86.12 (85.50, 86.73)	83.14 (81.36, 84.93)			
Moderate risk	10.21 (9.59, 10.83)	10.14 (9.64, 10.63)	11.31 (9.72, 12.90)			
High risk	2.54 (2.32, 2.77)	2.49 (2.27, 2.70)	3.40 (2.65, 4.15)			
Very high risk	1.31 (1.20, 1.43)	1.26 (1.14, 1.38)	2.15 (1.60, 2.71)			
Diabetes (%)				633 (1.86)	< 0.0001	< 0.0001
No	81.46 (77.84, 85.08)	81.87 (81.14, 82.59)	75.32 (73.35, 77.28)			
Diabetes	13.38 (12.62, 14.13)	12.97 (12.37, 13.58)	19.57 (17.75, 21.40)			
IGT	5.16 (4.74, 5.58)	5.16 (4.81, 5.51)	5.11 (4.04, 6.18)			
Hyperlipidemia (%)				1 (0.00)	0.0001	0.0001
No	29.30 (27.96, 30.63)	29.68 (28.71, 30.64)	23.51 (20.49, 26.53)			
Yes	70.70 (67.29, 74.12)	70.32 (69.36, 71.29)	76.49 (73.47, 79.51)			
Parkinson (%)				18 (0.05)	< 0.0001	0.0001
No	99.03 (94.81, 103.25)	99.17 (99.02, 99.32)	96.91 (95.87, 97.95)			
Yes	0.97 (0.80, 1.14)	0.83 (0.68, 0.98)	3.09 (2.05, 4.13)			

Data are expressed as weighted proportions (95% CI) for categorical variables and as weighted means (95% CI) for continuous variables.
CHD, coronary heart disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; IGT, impaired glucose tolerance; PHQ-9, the nine-item Patient Health Questionnaire.
[a]Two-sided *P*-values show result of univariate comparisons between depressed participants and participants who were not depressed. All categorical variables were tested with the χ^2-test.

14.34 million, 6.41 million, and 5.28 million adults in the general population, respectively.

The sociodemographic and clinical characteristics among the weighted population are shown in Table 1. Of note, depression was especially prevalent among those who were Black, female participants, in the 41–60 age bracket, from disadvantaged socio-economic backgrounds (marital status other than married, lower levels of education, lower family income, etc.), current smokers, extremely obese, and those who were more likely to be comorbid with CHD, stroke, hypertension, CHF, angina, heart attack, arthritis, CKD, COPD, diabetes, hyperlipidemia, and Parkinson's disease compared to the non-depression group.

Characteristic	OR (95% CI)	P Value	q Value	P for interaction
Gender				0.079
Male	1.42 (0.97 to 2.08)	0.073	0.073	
Female	2.24 (1.61 to 3.13)	<0.001	<0.001	
Age				0.345
[20,30]	9.56 (1.51 to 60.57)	0.018	0.037	
[31,40]	5.00 (1.50 to 16.67)	0.010	0.037	
[41,50]	1.73 (0.64 to 4.70)	0.284	0.284	
[51,60]	1.99 (1.10 to 3.61)	0.026	0.039	
[61,70]	2.03 (1.17 to 3.51)	0.013	0.037	
[71,85]	1.39 (0.91 to 2.13)	0.134	0.161	
Ethnicity				0.097
White	1.46 (1.05 to 2.04)	0.026	0.026	
Black	1.95 (1.15 to 3.28)	0.014	0.019	
Mexican	3.17 (1.74 to 5.75)	<0.001	0.001	
Other	2.28 (1.43 to 3.62)	<0.001	0.001	
Marital Status				0.542
Married	1.67 (1.19 to 2.35)	0.004	0.023	
Living with Partner	0.62 (0.19 to 2.05)	0.435	0.522	
Separated	0.96 (0.23 to 3.91)	0.951	0.951	
Divorced	1.53 (0.72 to 3.22)	0.270	0.405	
Widowed	1.91 (1.08 to 3.37)	0.028	0.081	
Never Married	2.81 (1.06 to 7.48)	0.041	0.081	
Educational Level				0.37
College Graduate or above	1.07 (0.43 to 2.65)	0.888	0.888	
Some College or AA Degree	1.96 (1.19 to 3.25)	0.010	0.049	
High School Graduate	1.07 (0.60 to 1.91)	0.822	0.888	
9-11th Grade	1.52 (0.95 to 2.42)	0.075	0.126	
Less than 9th Grade	1.63 (0.97 to 2.72)	0.065	0.126	
Poverty Income Ratio				0.201
High Income	0.71 (0.26 to 1.90)	0.492	0.492	
Middle Income	1.32 (0.68 to 2.54)	0.414	0.492	
Nearly Poor	1.96 (1.34 to 2.86)	<0.001	0.003	
Poor	1.76 (1.18 to 2.62)	0.007	0.017	
Unknown	2.48 (0.95 to 6.46)	0.066	0.109	
Smoking Status				0.424
Never	1.60 (1.02 to 2.50)	0.041	0.062	
Former	1.25 (0.77 to 2.03)	0.372	0.372	
Current	1.90 (1.22 to 2.97)	0.006	0.017	
Body Mass Index				0.881
Normal	1.40 (0.90 to 2.19)	0.137	0.206	
Overweight	1.58 (1.18 to 2.11)	0.003	0.008	
Low	1.99 (0.22 to 17.88)	0.541	0.541	
Overall	1.58 (1.22 to 2.06)	<0.001		

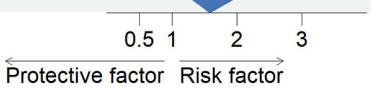

FIGURE 1
The association between depression and coronary heart disease risk in each subgroups. OR, odds ratio; CI, confidence interval.

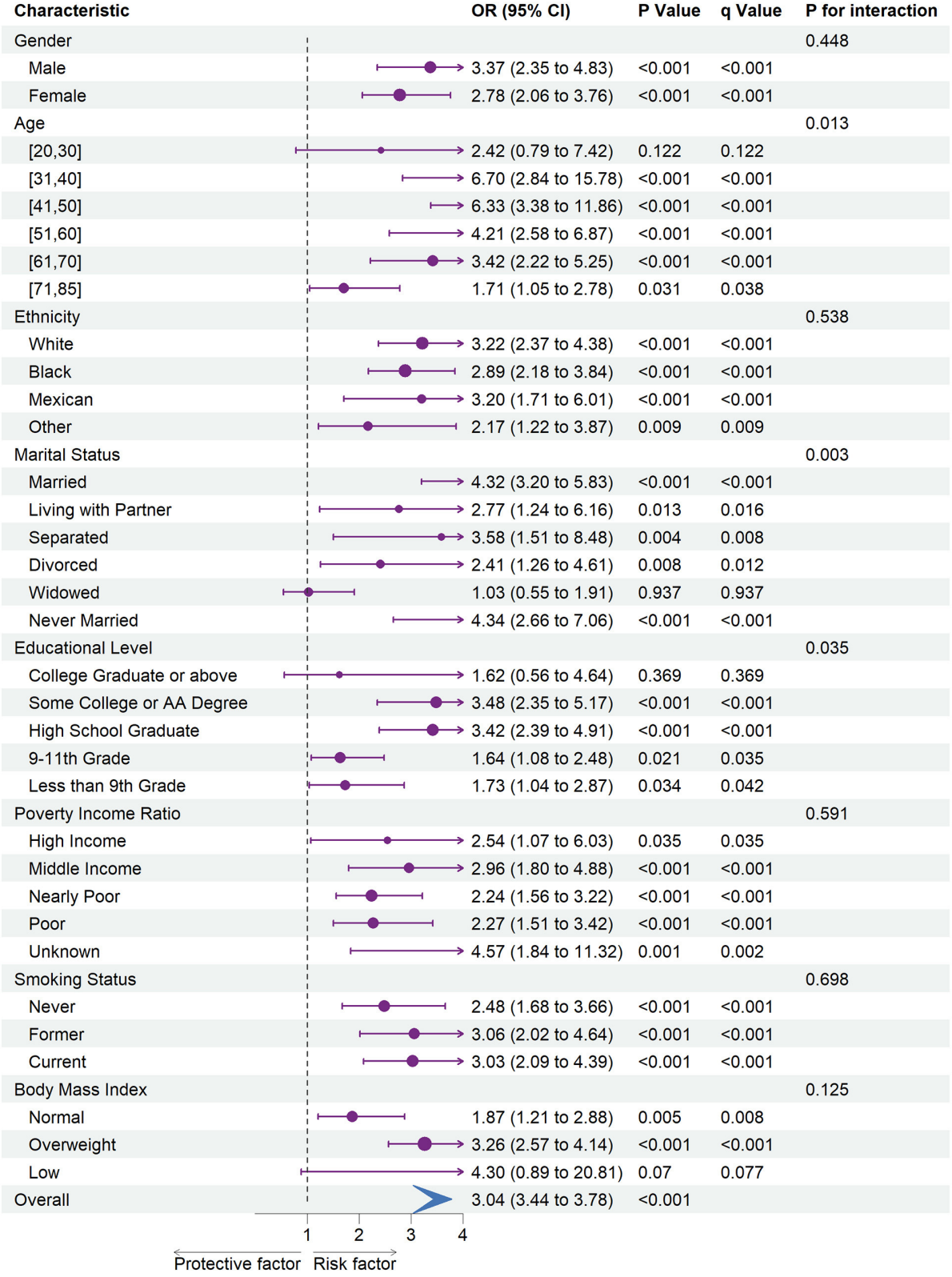

FIGURE 2
The association between depression and stroke risk in each subgroups. OR, odds ratio; CI, confidence interval.

TABLE 2 Crude and adjusted association between depression level and increased coronary heart disease and stroke risk.

Model	Severity of depression					*P* value for trend
	No/minimal prevalence = 77.24 (73.71,80.77)	Mild prevalence = 15.17 (14.42, 15.92)	Moderate prevalence = 4.83 (4.44, 5.22)	Moderately severe prevalence = 1.98 (1.76, 2.20)	Severe prevalence = 0.78 (0.67, 0.88)	
Coronary heart disease						
Model 1 (or)	1.00 (Reference)	1.19 (0.92 to 1.53)	1.76 (1.27 to 2.46)	1.47 (0.95 to 2.27)	2.55 (1.54 to 4.23)	<0.001
Raw *p* values		0.181	0.001	0.086	<0.001	
q value		0.181	0.002	0.114	0.002	
Model 2 (or)	1.00 (Reference)	1.50 (1.16 to 1.94)	2.55 (1.77 to 3.68)	2.09 (1.36 to 3.22)	4.58 (2.50 to 8.37)	<0.001
Raw p value		0.003	<0.001	0.001	<0.001	
q value		0.003	<0.001	0.002	<0.001	
Model 3 (or)	1.00 (Reference)	1.38 (1.06 to 1.79)	2.20 (1.53 to 3.16)	1.84 (1.20 to 2.81)	3.75 (2.07 to 6.78)	<0.001
Raw *p* values		0.019	<0.001	0.007	<0.001	
q value		0.019	<0.001	0.009	<0.001	
Stroke						
Model 1 (or)	1.00 (Reference)	1.95 (1.61 to 2.35)	2.72 (2.01 to 3.69)	3.77 (2.67 to 5.32)	5.94 (3.91 to 9.02)	<0.001
Raw *p* values		<0.001	<0.001	<0.001	<0.001	
q value		<0.001	<0.001	<0.001	<0.001	
Model 2 (or)	1.00 (Reference)	2.09 (1.72 to 2.53)	3.16 (2.28 to 4.39)	4.62 (3.18 to 6.69)	7.86 (5.08 to 12.16)	<0.001
Raw *p* value		<0.001	<0.001	<0.001	<0.001	
q value		<0.001	<0.001	<0.001	<0.001	
Model 3 (or)	1.00 (Reference)	1.79 (1.47 to 2.18)	2.37 (1.69 to 3.32)	3.36 (2.26 to 4.98)	5.37 (3.42 to 8.44)	<0.001
Raw *p* values		<0.001	<0.001	<0.001	<0.001	
q value		<0.001	<0.001	<0.001	<0.001	

Data are expressed as weighted means (95% CI) for continuous variables.
Model 1: Unadjusted model.
Model 2: Adjusted for age, gender, and ethnicity.
Model 3: Adjusted for age, gender, ethnicity, marital status, family PIR, education, smoking status, and BMI.
OR, odds ratio; PIR, poverty income ratio; BMI, body mass index.

Subgroup analyses

Figures 1, 2 shows the results of subgroup analysis using univariable weighted logistic regression analyses.

Subgroup analysis revealed an increased risk of CHD (OR = 1.58; 95% CI = 1.22 to 2.06) and stroke (OR = 3.04; 95% CI = 3.44 to 3.78) associated with depression in overall participants. Specifically, an increased risk of CHD was associated with depression in female participants, every ethnic group, and among participants of the age ranges 20–30, 31–40, 51–60, or 61–70. Besides, we also observed an increased risk of CHD associated with depression in participants whose marital status was married, widowed, or never married, whose education level was some college or AA degree, whose family PIR was nearly poor or poor, whose smoking status was never or current, and whose BMI was categorized as overweight.

Moreover, an increased risk of stroke was associated with depression within each gender, ethnicity, family PIR, smoking status, and among participants aged range from 31 to 85. Besides, we found that stroke risk was not associated with depression, among participants whose education level was college graduate or above, whose marital status was widowed, or whose BMI was categorized as low.

In subgroup analyses (Figures 1, 2), statistically significant interactions were not observed between depression and any study covariates in relation to CHD (all P for interaction > 0.05), but statistically significant interactions were noted between depression and age, marital status, and education level in relation to stroke (P for interaction = 0.013, 0.003, 0.035, respectively) despite the lack of interaction for other variables.

The association of depression level with CHD, stroke risk

Results of weighted logistic regression analyses of depression severity in relation to the risk of CHD and stroke are shown in Table 2. There was a statistically significant association between depression severity and increased risk of CHD and stroke in models 1, 2, and 3, and those linear trend tests were all statistically significant (all *P* for trend < 0.001). For example, the

result in model 3 showed that the risk of having CHD increased by 38, 120, 84, and 275% for mild, moderate, moderately severe, or severe depression, respectively, compared to no/minimal depression. Similarly, weighted logistic regression model 3 indicated that each additional level increase in the severity of depression raised the risks of stroke by 79, 137, 236, and 437%, respectively after adjustment for covariates.

Cause-specific mortality analyses

The leading causes of death in different depression severity groups are shown in Table 3. Among them, cardiovascular mortality rates were 1.91, 2.46, 2.78, 2.94, and 1.05% for no/minimal, mild, moderate, moderately severe, or severe depression, respectively. Moreover, the prevalence of all-cause mortality was 6.62, 8.60, 9.48, 10.77, and 10.42% for no/minimal, mild, moderate, moderately severe, and severe depression, respectively.

Survival analysis

All the participants were followed up after the home interview. After excluding the participants with CVDs, cancer, or malignancy at baseline in the survival analyses, the median follow-up time in the population-based cohort was 92.00 months (interquartile range: 52–132 months).

The weighted Cox regression analysis results are shown in Tables 4, 5, performed to estimate the relationships between the severity of depression and their risk of having all-cause and cardiovascular mortality, respectively.

TABLE 3 The weighted percentages of leading causes of death in different depression severity groups.

Cause of death	No/Minimal	Mild	Moderate	Moderately severe	Severe
Diseases of heart (%)	534 (1.57)	145 (2.03)	54 (2.47)	21 (2.64)	5 (1.05)
Cerebrovascular diseases (%)	124 (0.34)	27 (0.43)	8 (0.31)	3 (0.30)	0 (0.00)
Influenza and pneumonia (%)	42 (0.12)	5 (0.06)	2 (0.11)	3 (0.27)	0 (0.00)
Chronic lower respiratory diseases (%)	106 (0.33)	40 (0.75)	11 (0.45)	9 (1.13)	2 (0.61)
Nephritis, nephrotic syndrome and nephrosis (%)	34 (0.08)	10 (0.14)	7 (0.25)	4 (0.51)	0 (0.00)
Diabetes mellitus (%)	68 (0.19)	21 (0.39)	9 (0.63)	3 (0.19)	2 (0.69)
Malignant neoplasms (%)	555 (1.77)	119 (1.88)	43 (1.73)	15 (1.51)	7 (1.25)
Alzheimer's disease (%)	64 (0.19)	12 (0.15)	1 (0.02)	0 (0.00)	0 (0.00)
Accidents (unintentional injuries) (%)	62 (0.24)	15 (0.34)	4 (0.16)	2 (0.45)	6 (1.79)
All other causes (residual) (%)	604 (1.79)	139 (2.43)	64 (3.35)	25 (3.77)	11 (5.03)
All-cause (%)	2,193 (6.62)	533 (8.60)	203 (9.48)	85 (10.77)	33 (10.42)

Data are expressed as sample sizes (weighted percentage) for continuous variables.
The unweighted sample consisted of 30918 participants and represented 189.00 million non-institutionalized residents of the United States.

TABLE 4 Crude and adjusted association between depression level and all-cause mortality.

Model	Severity of depression					*P* value for trend
	No/Minimal	Mild	Moderate	Moderately severe	Severe	
Model 1 (HR)	1.00 (Reference)	1.36 (1.11 to 1.67)	1.55 (1.20 to 2.01)	1.99 (1.34 to 2.94)	2.08 (1.08 to 4.00)	<0.001
P value		0.003	0.001	0.001	0.028	
q value		0.004	0.002	0.002	0.028	
Model 2 (HR)	1.00 (Reference)	1.63 (1.31 to 2.01)	1.99 (1.54 to 2.56)	2.67 (1.73 to 4.11)	3.25 (1.71 to 6.20)	<0.001
P values		<0.001	<0.001	<0.001	<0.001	
q value		<0.001	<0.001	<0.001	<0.001	
Model 3 (HR)	1.00 (Reference)	1.38 (1.11 to 1.72)	1.41 (1.09 to 1.82)	1.95 (1.30 to 2.93)	2.08 (1.03 to 4.23)	<0.001
P values		0.003	0.010	0.001	0.042	
q value		0.003	0.010	0.001	0.042	

Data are expressed as weighted means (95% CI) for continuous variables.
Model 1: Unadjusted model.
Model 2: Adjusted for age, gender, and ethnicity.
Model 3: Adjusted for age, gender, ethnicity, marital status, family PIR, education, smoking status, and BMI.
HR, hazard ratio; PIR, poverty income ratio; BMI, body mass index.

TABLE 5 Crude and adjusted association between depression level and cardiovascular mortality.

Model	Severity of depression				
	No/minimal	Mild	Moderate	Moderately severe	Severe
Model 1 (HR)	1.00 (Reference)	1.47 (1.18 to 1.83)	1.74 (1.20 to 2.52)	2.07 (1.22 to 3.50)	0.85 (0.30 to 2.43)
P value		0.001	0.004	0.007	0.758
q value		0.002	0.007	0.009	0.758
Model 2 (HR)	1.00 (Reference)	1.75 (1.38 to 2.22)	2.27 (1.57 to 3.30)	3.06 (1.81 to 5.16)	1.36 (0.45 to 4.09)
P value		<0.001	<0.001	<0.001	0.586
q value		<0.001	<0.001	<0.001	0.586
Model 3 (HR)	1.00 (Reference)	1.49 (1.16 to 1.91)	1.68 (1.15 to 2.45)	2.37 (1.39 to 4.06)	0.89 (0.29 to 2.76)
P value		0.002	0.007	0.002	0.845
q value		0.003	0.010	0.003	0.845

Data are expressed as weighted means (95% CI) for continuous variables.
Model 1: Unadjusted model.
Model 2: Adjusted for age, gender, and ethnicity.
Model 3: Adjusted for age, gender, ethnicity, marital status, family PIR, education, smoking status, and BMI.
HR, hazard ratio; PIR, poverty income ratio; BMI, body mass index.

The results from a series of weighted Cox regression analyses in Table 4 consistently indicated that participants with a more severe degree of depression were at a higher risk of all-cause death. For instance, weighted multivariable Cox proportional hazard model 3 indicated that each additional level increase in the severity of depression raised the risks of all-cause death by 38, 41, 95, and 108%, respectively, after adjustment for covariates. Trend analyses were all statistically significant (all P for trend < 0.001).

However, a series of weighted Cox regression analysis results in Table 5 consistently suggests that with the exception of severe depression, the hazard of cardiovascular mortality increased with each additional level increase of depression. Using weighted multivariable Cox proportional hazard model 3 as an example, compared to no/minimal depression, the risks of cardiovascular death were increased by 49, 68, and 137% for mild, moderate, and moderately severe depression, respectively, after multivariable adjustment.

Moreover, the unadjusted survival curves of weighted Cox proportional hazards models for all-cause and cardiovascular mortality (Figures 3, 4) were consistent with the aforementioned findings.

Discussion

In our study, performed on a nationally representative cohort of the United States population, we found that the level of depression was independently associated with higher risk of having CHD, stroke, and all-cause and cardiovascular mortality.

Cardiovascular diseases are often comorbid with depression. Cohen et al. reported that 20% of patients with CVDs had moderate to severe depression, and another 20% of patients with CVDs had mild to moderate depression, which is approximately two to three times the rate of the general population (30). In addition, a meta-analysis with a median follow-up of 8.4 years revealed that the cumulative incidence of CVDs in patients with severe mental illness (SMI) was 3.6% (95% CI = 2.7% to 5.3%), which was significantly higher than in people without SMI (HR = 1.78; 95% CI = 1.60 to 1.80); compared to the control group, patients with depression had 1.72 times the risk of CVDs after controlling for confounding variables (31).

The mechanisms underlying the common dual comorbidities of depression and CVDs were complex, and current research suggested that depression and CVDs may be linked by biological and behavioral mechanisms, including *via* metabolic syndrome—which is prevalent in depression, type 2 diabetes, increased visceral adipose thickness, changes in cortisol levels due to the dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis and unhealthy lifestyle habits (smoking, poor diet, lack of exercise, etc.) (32–37). Moreover, in recent years, studies also reported that cardiovascular traits such as blood pressure and arterial stiffness were influenced by and associated with depression (38, 39). Of note is a recent study by Mutz et al., which reported that depression resulted in a 1 mmHg lower systolic blood pressure (SBP) at age 45 and a 2.5 mmHg lower SBP at age 65 in male participants (38). However, it was also worth noting that the mean values of SBP in male participants were all near 140 mmHg, whether in healthy control or depression case in that study. In this context, the effect of such a small SBP difference on the coronary arteries was negligible in male participants. Thus, the present study is not in contradiction with the Mutz et al. study. In addition, studies have shown that these two diseases may be driven by a common genetic susceptibility, and each disease increased the risk of the other (40).

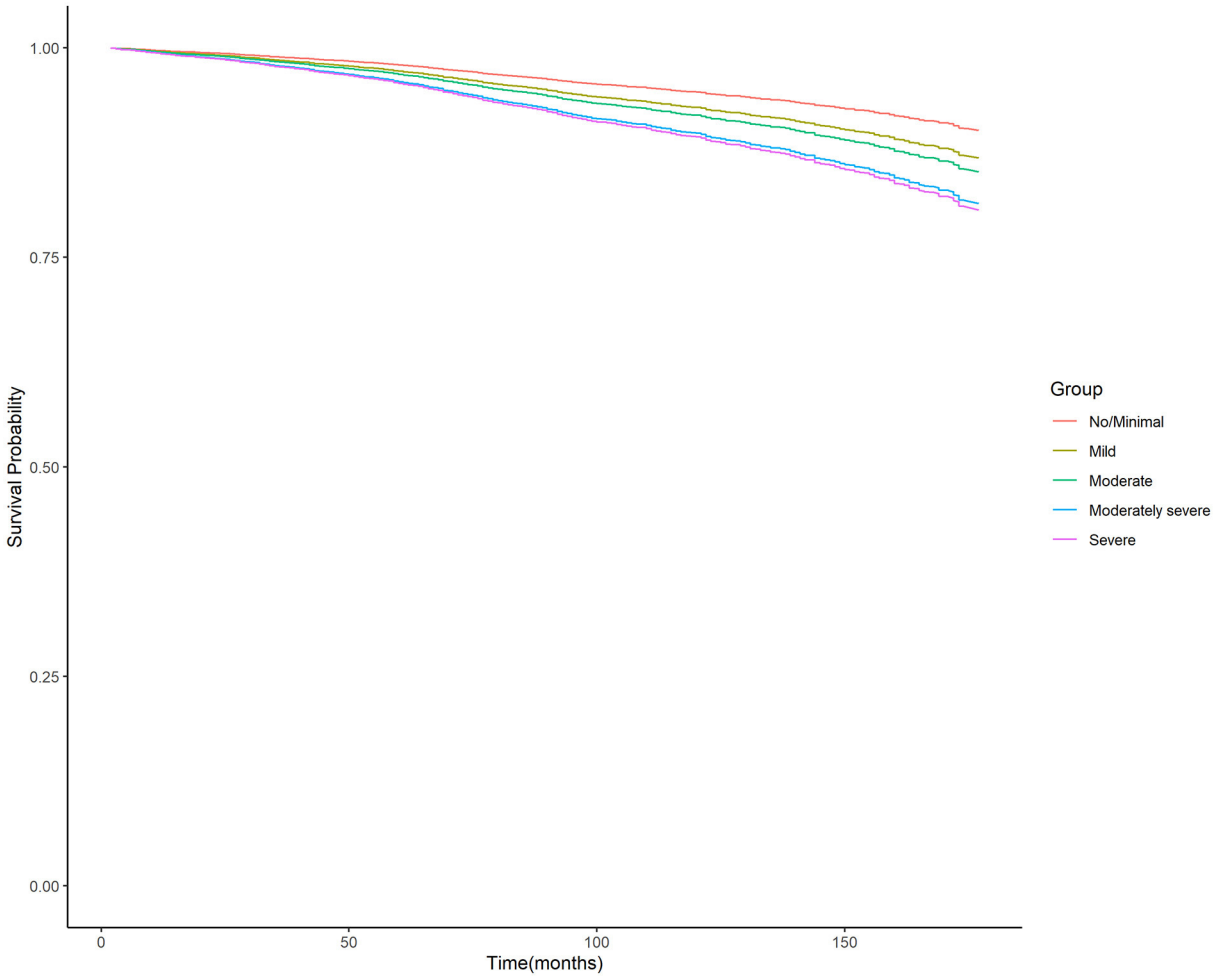

FIGURE 3
Unadjusted survival curves of weighted cox proportional hazard model for all-cause mortality. PHQ-9, nine-item Patient Health Questionnaire.

Previous studies had demonstrated that depression was identified as a risk factor for CVDs (41), while the association between specific severity of depression and CHD, stroke risk as well as mortality is still unknown. For this reason, further research was undertaken in this study, and we found out that with each additional level increase of depression, the implications of such an increase in the risk of having CHD, stroke, and mortality were vast.

Therefore, by understanding the relationship and degree of impact, we can properly identify, prevent, and treat CVDs, and we will be able to create policies and strategies to help decrease CVDs and improve lives by tackling mental health. This emphasizes the importance of regular screening for cardiovascular risk factors in patients with depression.

Interestingly, we also observed that participants with higher depression levels had a higher risk of all-cause mortality; a previous study showed that the mortality for depression patients with concomitant CVD whose depression was well-treated, treatment-resistance, and under-treated were 2.4, 5, and 6.9%, respectively (42, 43). These findings suggested that enhanced depression treatment reduces the risk of death.

In analyses of the association between depression level and cardiovascular death, we found that the hazard of cardiovascular death was the lowest in the severe depression group. This phenomenon may be explained by the result of the death cause analysis in our study. We found that the leading cause in this group was all other causes (residual) (5.03%) followed by accidents (unintentional injuries) (1.79%), malignant neoplasms (1.25%), and heart diseases (1.05%).

In summary, patients with depression may need early and/or more primary prevention efforts for CVDs to reduce their excessive CVDs burden. For clinicians, this means a need for effective collaboration with primary care clinicians and cardiologists. Early treatment is more likely to modify the risk

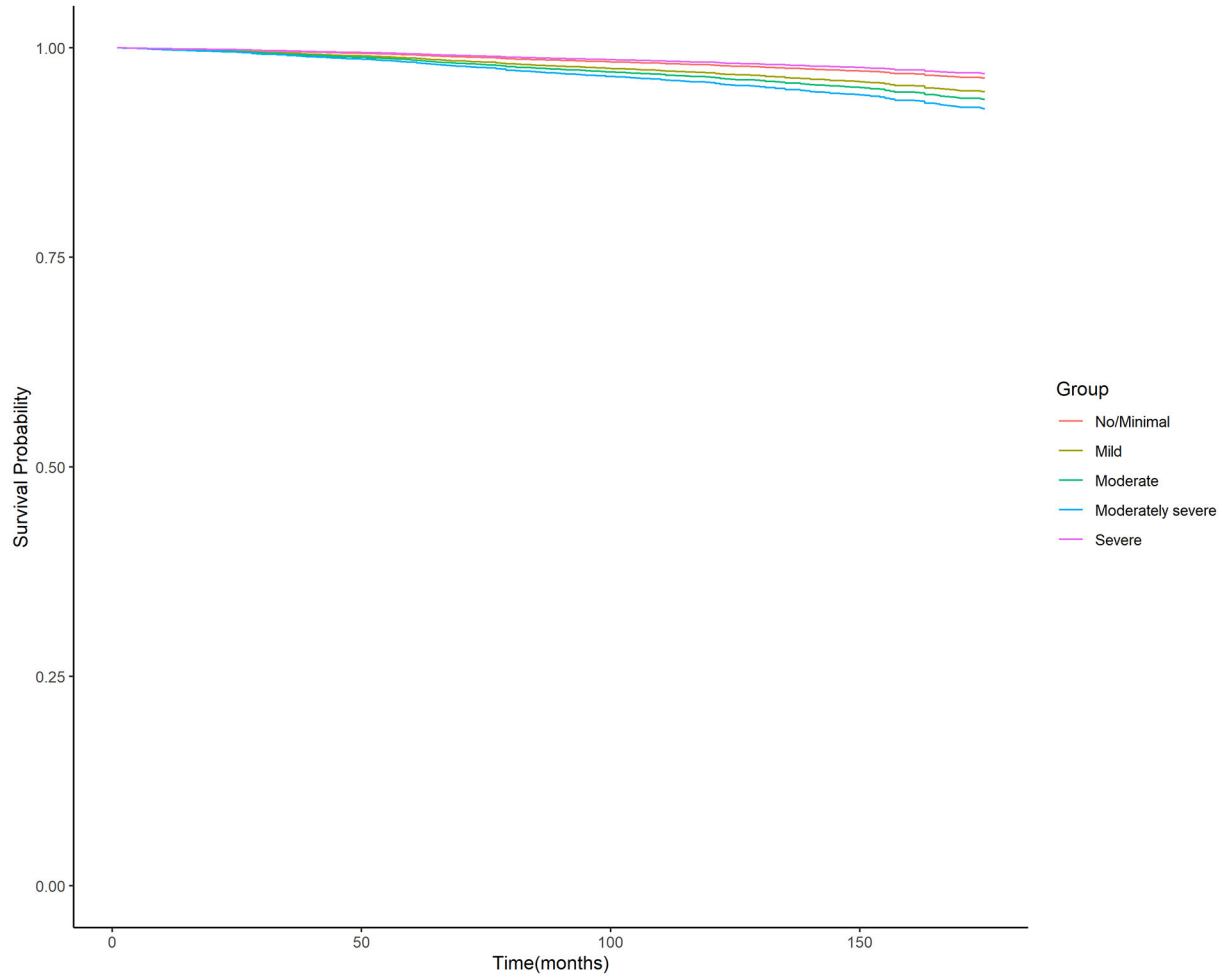

FIGURE 4
Unadjusted survival curves of weighted cox proportional hazard model for cardiovascular mortality. PHQ-9, nine-item Patient Health Questionnaire.

factor in the progression of cardiac disease than to reverse these risk factors after the first heart attack (36).

Systematic monitoring of depression was particularly beneficial in cases where physical illness overlaps with depressive symptoms (44). Serial assessment of depressive symptoms with the PHQ-9 or similar methods can improve the efficiency of antidepressant treatment. It also documents the relationship between depressive symptoms and specific physiological indicators of CVDs (45).

It follows then that the first limitation in our study is that PHQ-9 was measured only once and was not followed up for subsequent changes in depression level, cumulative depression burden, incident depression, or time-varying associations with outcomes.

Second, some measures in this study, including the diagnosis of CHD, stroke, and any symptoms of depression in PHQ-9, were self-reported by the participants, which may have introduced recall bias to the associations.

Third, the NHANES program suspended field operations in March 2020 due to the coronavirus disease 2019 (COVID-19) pandemic. As a result, data collection for the NHANES 2019–2020 cycle was not completed and the collected data are not nationally representative, and the PHQ-9 information had not been included in the home interview since 2005, As a result, we only included participants from 2005 to 2018.

Fourth, the application of the competitive risk model in the survival analyses cannot be performed due to the complex, stratified multistage, probability cluster design of the NHANES survey.

Fifth, some of the covariates included as covariates in the multivariable-adjusted model (e.g., BMI) were likely on the causal pathway linking depression to cardiovascular outcomes.

Therefore, interpretation of the present findings needs to also consider the risk of potential over adjustment bias.

Conclusion

In conclusion, our study confirmed that the level of depression was strongly associated with CHD, stroke, and all-cause and cardiovascular mortality, even after accounting for other factors that could impact risk, including variables of age, gender, ethnicity, income, education, BMI, marital, and smoking status.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://www.cdc.gov/nchs/nhanes/index.htm and https://www.cdc.gov/nchs/data-linkage/mortality-public.htm.

Ethics statement

The studies involving human participants were reviewed and approved by the NCHS Research Ethics Review Board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

RS had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: RS, NZ, and JW. Drafting of the manuscript: RS and NZ. Critical revision of the manuscript for important intellectual content: RS, NZ, TZ, JW, PG, and SS. Statistical analysis: RS and SS. Obtained funding and supervision: TZ. Administrative, technical, or material support: TZ, DL, and PG. Acquisition, analysis, or interpretation of data: all authors. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Dawning public health services dogma: An indigenous Southwest Chinese perspective in managing hypertension-with or without the "BPHS"?

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Background: To alleviate the rising mortality burden due to hypertension and other non-communicable diseases, a new public health policy initiative in 2009 called the Basic Public Health Services (BPHS). Program was introduced by the Chinese government. The goal of the study is to assess the feasibility and impact of a nationwide health care service—the "BPHS".

Methods: From January to December 2021, a stratified multistage random sampling method in the survey was conducted to select 6,456 people from 8 cities/districts in Yunnan Province, China, who were above the age of 35 years. 1,521 hypertensive patients were previously aware of their high blood pressure status were matched to the BPHS program database based on ID number and then further divided into BPHS group and non-BPHS (control) group. The results of the current study are based on their responses to a short structured questionnaire, a physical examination, and laboratory tests. The association between BPHS management and its effect on the control of hypertension was estimated using multivariable logistic regression models. We evaluated the accessibility and efficacy of BPHS health care services by analyzing various variables such as blood pressure, BMI, lifestyle modification, anti-hypertensive drugs taken, and cardiovascular risk factors.

Results: Among the 1,521 hypertensive patients included in this study, 1,011 (66.5%) were managed by BPHS programme. The multivariable logistic regression model demonstrated that the BPHS facilitated hypertension control (OR = 1.640, 95% CI: 1.237–2.175). A higher proportion of participants receiving lifestyle guidance from the BPHS management showed lowering of total cholesterol. In comparison to the non-BPHS group, those under BPHS management adhered better to antihypertensive medications either single

drug (54.3%) or in combination (17.3%) of drugs. Additionally, we also noticed that urban areas with centralized and well-established digital information management system had better hypertension treatment and control.

Conclusions: Nearly two-thirds of the hypertensive patients in Yunnan Province were included in BPHS management. The impact of the national BPHS program was evident in lowering risk factors for cardiovascular diseases, promoting healthy lifestyles, lowering blood pressure, increasing medication adherence, and the better control rate of hypertension.

KEYWORDS

basic public health service, hypertension management, effectiveness and quality, low and middle-income countries, health policy

Introduction

The number of people with hypertension increases from 650 to 1.28 billion worldwide from 1990 to 2019 in the age group of 30–79 years (1). Hypertension has become the major cause of premature mortality and cardiovascular disease (CVD) globally (2). The Global Burden of Disease Study reported that hypertension was the primary risk factor for all deaths globally, accounting for 19.2% (10.8 million) of all mortality worldwide in 2019 (3). About 245.5 million people are affected by hypertension in China (4), and hypertension is estimated to cause 2.54 million deaths in 2017, with 95.7% of these deaths being due to CVD (5).

Controlling blood pressure to a normal state reduces the risk of cardiovascular events and all-cause mortality (6–8). The trend of cardiovascular disease will be directly impacted by how hypertension is managed in primary medical and health organizations (community health centers, township health centers, and village clinics) (9). Global studies have demonstrated that primary health care (PHC) was better effective in hypertension management and improved blood pressure control (10–14).

In 2009, China's new healthcare reform introduced the "National Basic Public Health Service Program" (BPHS), which provides free of cost health services throughout the country by partnering with community health organizations. The management of hypertensive patients aged 35 and over was one of the 12 kinds of voluntary free services contents in BPHS (15, 16), including screenings, lifestyle guidance for hypertensive patients, at least four in-person follow-up visits per year, risk factor intervention, health education promotion, health examination, referral services, guidance on the use of antihypertensive medicine, and personal health record establishment (17, 18). With BPHS, 35.1% of hypertensive patients have received four or more follow-up assessments in the past 1 year (19), uncontrolled hypertension was reduced by 26% (20). However, most of the earlier studies on being covered by BPHS were self-reported by participants, and focused on the rate of service delivery from primary doctors (21, 22), patient service satisfaction (23, 24) and the community health management rate of hypertensive patients (25, 26). Previous studies also showed a low prevalence of combination therapy and limited compliance with hypertension drug treatment (27, 28). Additionally, the hypertensive control rate is only 15.3% in China (4), and more than 50% of hypertension patients had multiple CVD risk factors, which can affect hypertension control (27, 29).

This study comprehensively evaluated the BPHS hypertension management in Yunnan Province, a relatively economically backward in southwest China. Hypertensive patients who were aware of their high blood pressure from a representative sampling survey and BPHS system matched, to compare matched BPHS group and unmatched non-BPHS groups' coverage and current hypertension status, CVD risk factors, management and effectiveness, blood pressure control rate and antihypertensive drug use, etc. This study supports the World Health Organization's (WHO) suggestion that developing nations should increase their access to management-controlled hypertension-related healthcare services (30). Rarely are there extensive comparisons of BPHS and non-BPHS groups' effects on hypertension management based on unique ID matching published.

Methods

Study design and sampling procedures

The survey was conducted in Yunnan province from January to December 2021, and samples were chosen using a stratified multistage random sampling method. As shown in Figure 1, all 129 counties and districts were separated into urban and rural sectors in the initial phase. The probability proportional to size (PPS) sampling was used to choose four districts in the urban areas (namely, Guandu, Zhaoyang, Mengzi, and

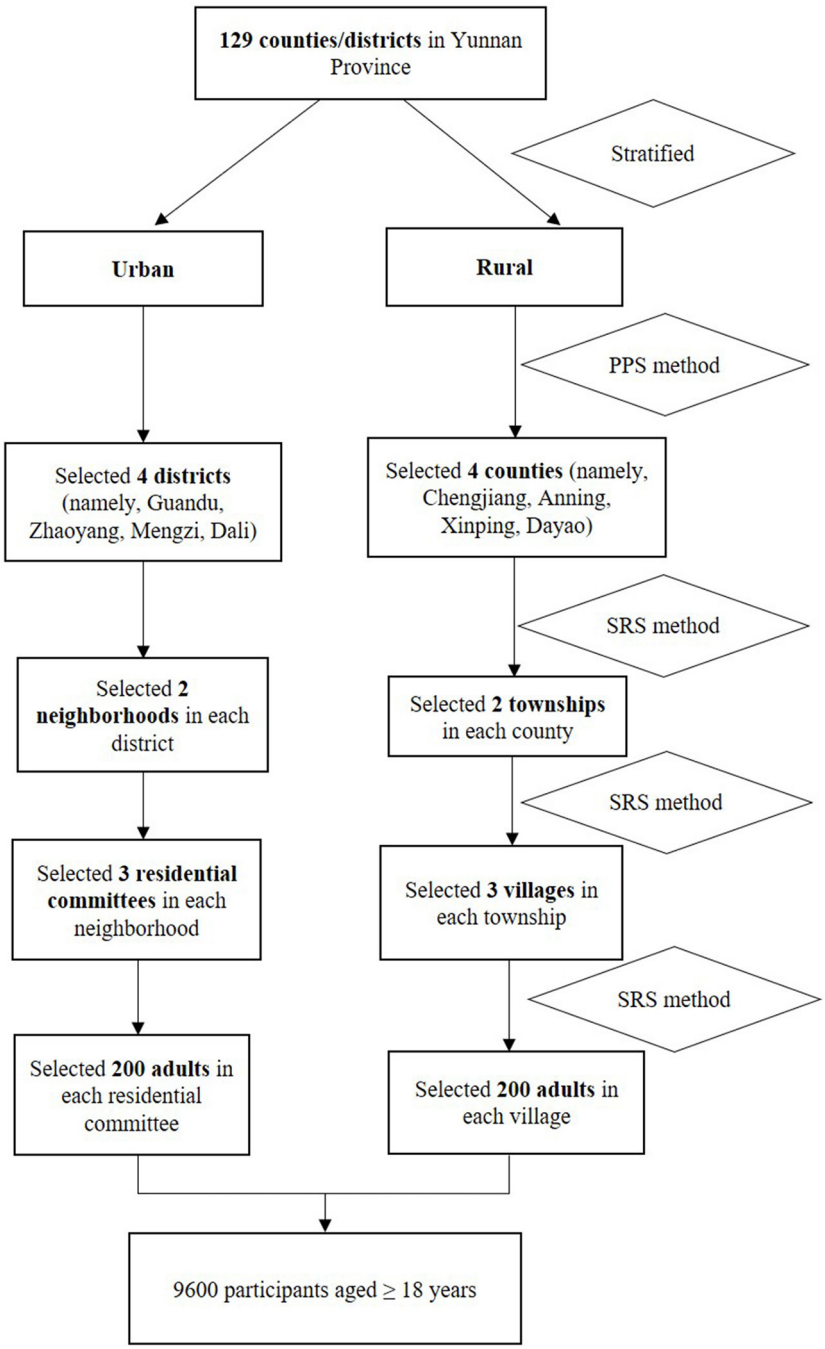

FIGURE 1
The Hypertension survey procedure of sampling. PPS, probability proportional to size; SRS, simple random sampling.

Dali) and four counties in the rural areas (namely, Chengjiang, Anning, Xinping, and Dayao). Then, two neighborhoods or two townships were randomly sampled in each district or county, respectively. Later, three residential committees or villages were randomly selected within each neighborhood and township, respectively. Finally, 9,600 individuals aged ≥18 years were selected from each chosen residential committee or village by the SRS method after considering the sex and age composition.

The target population for BPHS hypertension management is patients who are residents of the jurisdiction aged 35 years and older (17), so we excluded those who did not meet this age. Yunnan Province has established the BPHS electronic case system and hypertension case management package, and

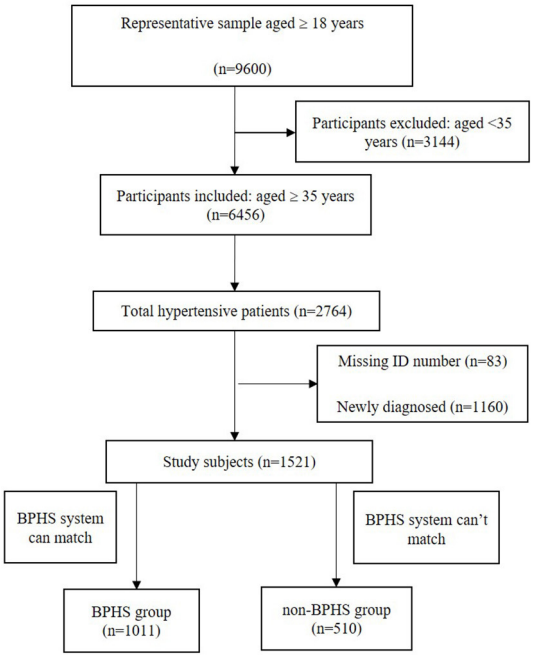

FIGURE 2
Flowchart of the participant selection process. BPHS, basic public health services.

patients' follow-up information has been uploaded to the database by primary care physicians based on the patient's unique ID card. Among the population aged ≥35 years 1,521 hypertensive patients who know their high blood pressure status, the unique ID number was matched with the BPHS electronic system, of which 1,011 patients were matched and included in BPHS hypertension management and 510 patients were not included, who were allocated to non-BPHS group (Figure 2).

Data collection

After receiving sufficient training, the medical staff will serve as the investigation team, using a unified work plan and investigation equipment. After informed consent, basic information was gathered *via* face-to-face short structured questionnaires that included details of their socio-demographics like age, gender, ethnicity, place of residence, educational attainment, occupation, annual household income, and wellness behaviors like smoking, drinking, dieting, exercising, and finally about hypertension perse like the history of hypertension, treatment followed from the time of diagnosis. Additionally, we measured height with RGZ-160 measuring instrument (Jiangsu Suhong Medical Instruments Co., Ltd., Jiangsu, China), and body weight was measured with an InBody H20B (InBody Co., Ltd., Seoul, South Korea) removing shoes, hats, coats, or weight in pockets. Body mass index (BMI) is a person's weight (kg) divided by the square of height (m) (31).

Diastolic blood pressure (DBP) and systolic blood pressure (SBP) were measured in the right upper arm using an OMRON HBP-1,300 (Omron Healthcare Co., Ltd., Kyoto, Japan) at 5 min intervals; three readings were recorded and the average of the three measurements was used for this study. In the meantime, participants were asked to fast for more than 8 h before collecting 8 ml of blood samples for cryopreservation and then sent to Beijing ZhongtongLanbo Medical Test Laboratory for measurement of triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and total cholesterol (TC). The findings and readings were recorded on the iPad in specially designed survey tables (see Supplementary File 1), and the investigation process was summarized in Supplementary File 2 and Supplementary Video.

Definition

According to the 2018 Chinese Guidelines (29) and 2020 International Society of Hypertension (ISH). Global Hypertension Practice Guidelines (27), hypertension was defined as mean SBP ≥140 mm Hg and/or mean DBP ≥90 mm Hg, or self-reported use of blood pressure control drugs in the past 2 weeks. Hypertension control was defined as mean SBP <140 mm Hg and DBP <90 mm Hg (29). The antihypertensive drug classification was also consistent with the guidelines. Based on the Chinese guidelines on prevention and treatment of dyslipidemia in adults (32), defined high TG, high TC, high LDL-C, and low HDL-C as ≥2.26, ≥6.22, ≥4.14, <1.04 mmol/L, respectively.

People who smoked more than one cigarette per day for more than 6 months were considered "current smokers" (33). Participants drinking alcohol at least once a week were classified as "current drinkers" (34). <150 min of moderate-intensity physical activity per week was defined as insufficient physical activity (35). Participants who consumed an average of <400 g of fruits and vegetables per day were insufficient intake (36). According to the recommended criteria for obesity in Chinese (31), overweight was defined as a person's BMI between 23 and 24.9 kg/m^2, obesity was a BMI of 25 kg/m^2 and above. Risk factors for cardiovascular disease (CVD) as per 2020 ISH Guidelines (27) were people who smoke, drink, don't eat enough vegetables and fruits, don't get enough exercise, are overweight, or are obese.

Statistical analyses

All statistical analyses use IBM SPSS 22.0 (SPSS Inc., New York, NY, USA). Categorical variables from the BPHS and non-BPHS groups were presented as numbers (proportions), and

differences between groups were compared using the chi-square test or Fisher's exact test. Mean ± standard deviation (SD) and *t*-tests were used for normally distributed continuous variables. Four indicators of blood lipids (TG, TC, HDL-C, and LDL-C) were skewed distribution data by Kolmogorov-Smirnov test, described by median and inter quartile range, and the differences between groups were tested by Wilcoxon rank sum test.

Eleven characteristic variables as age (35–44, 45–54, 55–64, and ≥65 years), residence (urban and rural), gender (male and female), ethnicity (Han or other minorities), annual household income (<4,487 USD/year, ≥4,487 USD/year), education attainment (elementary school and below, junior high school and above), current smoker (yes or no), current drinker (yes or no), insufficient vegetable and fruit intake (yes or no), insufficient physical activity (yes or no), overweight and obesity (yes or no) were compared between the two groups.

The ggplot2 package of R 4.0.5 (The R Project for Statistical Computing, Vienna, Austria) was used to construct the visible distribution of blood pressure and a stacked column chart of "controlled with treatment", "treated but not controlled", and "diagnosed but untreated". Unadjusted and full adjusted binary logistic regression models were conducted to assess the association between hypertension control with BPHS, the first model did not adjust for potential influencing factors. Next, second model was performed to adjust for potential influencing factors, including age, gender, ethnicity, residence, household income and educational level. Then, the odds ratio (OR) and 95% confidence interval (CI) were estimated. All tests were two-sided and $p < 0.05$ was considered statistically significant.

Results

General description of participants

The mean age of the 1,521 hypertensive patients was 62.6 ± 12.6 years old, with 737 men (48.5%) and 858 people living in urban areas (56.4%), 1,118 Han people (73.5%), 1,104 people (72.6%) with an annual family income of <4,487 USD/year, and 898 people (59.0%) with primary school education or below (Table 1).

Demographic and CVD risk factors differences between the BPHS and non-BPHS groups

1011 (66.5%) and 510 (33.5%) hypertensive patients came from the BPHS and non-BPHS groups. Hypertensive patients included in BPHS management were more likely to be older, female, non-Han Chinese, and had lower family economics and literacy (all $p < 0.05$). Furthermore, the BPHS group had a lower proportion of current smokers and their consumption of fruits and vegetables was inadequate (all $p < 0.05$).

Blood pressure

As shown in Table 1, those who received BPHS management had significantly lower SBP and DBP than those who did not ($p < 0.001$), the average SBP was (146.8 ±18.8 vs. 149.7 ± 19.1) mm Hg, and DBP (85.7 ± 12.5 vs. 91.2 ± 12.7) mm Hg, respectively (all $p < 0.05$). The non-BPHS group showed greater variation in SBP and DBP distribution than the BPHS group (Figure 3). Furthermore, more than half of the patients did not receive antihypertensive medication in the non-BPHS group.

Control of hypertension

The BPHS group indicated higher hypertension control rate (33.2%) than the non-BPHS group (22.2%) shown in Table 2. Furthermore, model 1 (did not adjusted for independent variables), and model 2 (adjusted confounding variables) all showed a significantly higher hypertension control rate from the BPHS group (OR = 1.640, 95% CI: 1.237–2.175). Regardless of the age, those who received BPHS management had higher rates of hypertension control, as shown in Figure 4.

Comparison of BPHS and non-BPHS group lifestyle modification services and lipid levels

Among those hypertensive patients enrolled in BPHS, the percentages who had received lifestyle modification services on salt reduction guidance, regular physical activity, weight reduction, smoking cessation, alcohol restriction, and stress reduction guidance services were 89.5, 86.9, 84.6, 83.8, 84.1, and 81.3%, respectively, both higher than the non-BPHS group, with 81.7, 79.2, 77.4, 78.7, 78.3, 72.9%, respectively (chi-square test, $p < 0.05$) (Figure 5).

Further analysis proved that patients with BPHS had lower TC after receiving weight reduction guidance, smoking cessation guidance, and alcohol consumption restriction guidance than those who did not receive such services. In addition, patients who received weight loss, smoking cessation, alcohol consumption restriction, and stress guidance also had lower HDL-C, however within the normal range. No significant differences were observed in TG and LDL-C levels between those who received lifestyle modification services and those who did not (Table 3).

TABLE 1 Socio-demographic characteristics and distribution of CVD risk factors between the BPHS and non-BPHS groups in Yunnan, China.

Characteristics	Total ($n = 1,521$)	BPHS group ($n = 1,011$)	non-BPHS group ($n = 510$)	p-Value
Demographic and socioeconomic characteristics				
Age, (mean ± SD)[£]	62.6 ± 12.6	65.0 ± 12.1	57.8 ± 12.3	
35–44	134 (8.8)	52 (5.1)	82 (16.1)	<0.001
45–54	324 (21.3)	179 (17.7)	145 (28.4)	
55–64	365 (24.0)	233 (23.0)	132 (25.9)	
≥65	698 (45.9)	547 (54.1)	151 (29.6)	
Male sex	737 (48.5)	455 (45.0)	282 (55.3)	<0.001
Urban residence	858 (56.4)	558 (55.2)	300 (58.8)	0.178
Han people	1,118 (73.5)	716 (70.8)	402 (78.8)	0.001
Household income <4,487 USD/year	1,104 (72.6)	771 (76.3)	333 (65.3)	<0.001
Education, elementary school and below	898 (59.0)	654 (64.7)	244 (47.8)	<0.001
CVD risk factors				
Current smokers	223 (14.7)	135 (13.4)	88 (17.3)	0.042
Current drinkers	267 (17.6)	177 (17.5)	90 (17.6)	0.946
Insufficient vegetable and fruit intake	1,330 (87.4)	869 (86.0)	461 (90.4)	0.014
Inadequate physical activity	411 (27.0)	282 (27.9)	129 (25.3)	0.281
Overweight and obesity[#]	909 (66.3)	612 (66.0)	297 (66.7)	0.791
Blood pressure[£]				
SBP	147.8 ± 19.0	146.8 ± 18.8	149.7 ± 19.1	0.006
DBP	87.6 ± 12.8	85.7 ± 12.5	91.2 ± 12.7	<0.001
Blood pressure status				<0.001
Diagnosed but untreated	563 (37.0)	287 (28.4)	276 (54.1)	
Treated but uncontrolled	510 (33.5)	388 (38.4)	122 (23.9)	
Controlled	448 (29.5)	336 (33.2)	112 (22.0)	

CVD, cardiovascular diseases; SD, standard deviations; BPHS, basic public health services; BMI, body mass index.
[#]Height or weight data were not available for 226 participants.
[£]Mean ± standard deviation, t-test was used to compare the mean DBP and SBP of the BPHS group and the non-BPHS group.

Treatment patterns and hypertension control rate

In Table 4, among 1,011 hypertensive patients included in BPHS management, 724 (71.6%) took medication, 549 (54.3%) chose monotherapy, and 175 (17.3%) used a combination of antihypertension drugs. All the treatment proportions were higher than the patients without BPHS coverage. In patients without taking antihypertensive medication, the control rate was higher in the BPHS group compared with the non-BPHS group (26.1 vs. 9.8%, $p < 0.001$).

Blood pressure management status distributions among subjects

A lower blood pressure control rate was observed from male patients aged 65 years and above, especially at Dayao, Xinping, Anning, and Chengjiang counties in rural areas. In general, it was observed that, there was a higher prevalence of hypertension treatment and better control among women than men. Patients with hypertension of any gender who are older than 65 can access antihypertensive medications and have better control over their condition. There is no significant difference noticed between subjects with different income levels among the groups of "diagnosed but untreated," "treated but not controlled," and "controlled with treatment." (Figure 6).

Discussion

This study showed the status of BPHS coverage and the effectiveness in the management of hypertensive patients in Southwest China (Yunnan Province) was corroborated by provincial-specific investigation results. Patients' ID in the survey matched with the BPHS system and found that 66.5% of hypertensive patients were included in BPHS and received related management services. The accessibility of BPHS for hypertensive patients in Yunnan Province was higher than the national accessibility rate (26). BPHS in this province is a patient-centered system which has access to multiple

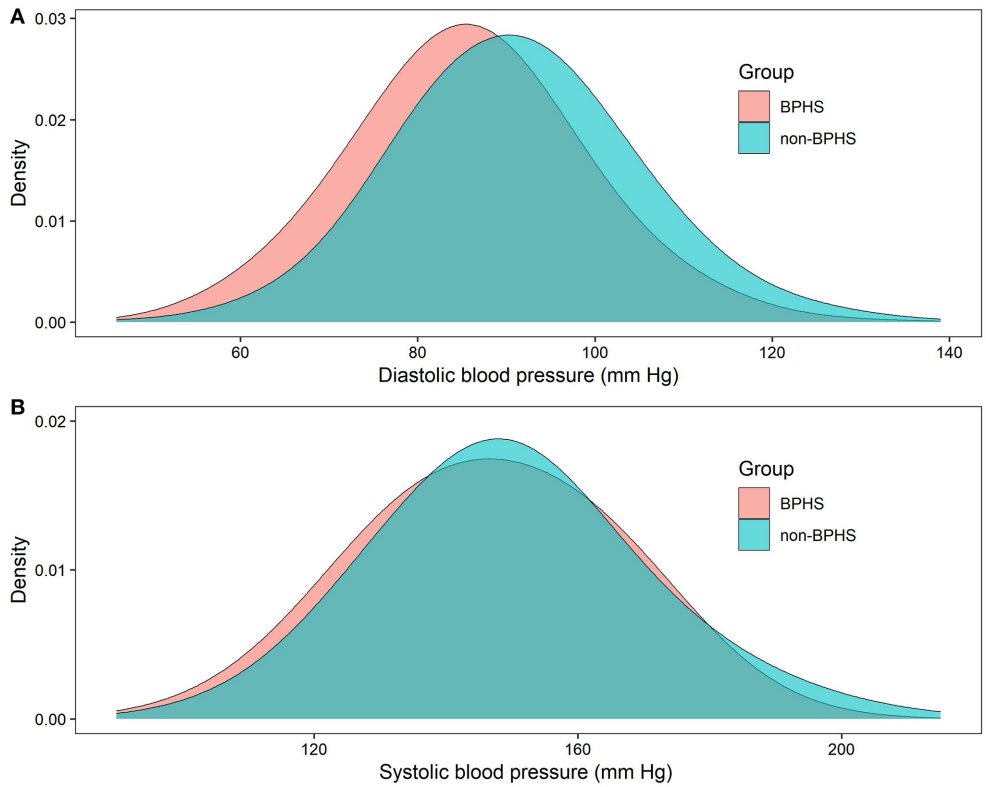

FIGURE 3
Distribution of DBP **(A)**, SBP **(B)** by BPHS and non-BPHS groups, in Yunnan China.

TABLE 2 Unadjusted and adjusted models: association of BPHS with control of hypertension.

	Control, *n* (%)	Model 1			Model 2		
		OR	95%*CI*	*p*-Value	*OR*	95%*CI*	*p*-Value
non-BPHS group	112 (22.2)	Ref	–	–	Ref	–	–
BPHS group	336 (33.2)	1.769	1.382–2.265	<0.001	1.640	1.237–2.175	0.001

BPHS, basic public health services.
Model 1 did not adjust for potential independent variables.
Model 2 adjusted confounding variables, including age, ethnicity, residence, gender, annual household income, and educational level.

medical databases (including medical institution outpatient and inpatient case databases, electronic medical examination records, etc.) and is thence based on individual care. Due of this well-organized system, more hypertensive patients will be identified proactively compared to other provinces. In the event a patient is identified as hypertensive by the system, a primary care physician will provide continuous BPHS management services. However, the BPHS accessibility rate was found to be lower than that in China's developed regions (90%) (37), as Yunnan province in southwest China has a relatively backward economy, 94% of its terrain is alpine, and 33% of its population is ethnic minority, which could be a plausible reason for relatively low BPHS access. The community uses BPHS or a comparable information system to compile data on daily medical services provided to the community, hypertension management and treatment results are yet to be improved with limited resources. In order to effectively treat all patients with hypertension, particularly in rural and remote regions of low-income provinces in southwest China, there is a need to enhance access to public and primary health services for these patients (12, 38). It is imperative that this regional gap in BPHS be addressed with utmost importance and urgency.

Uncontrolled hypertension may result in ~24,914,000 years of life lost and 28,657,000 quality-adjusted life years

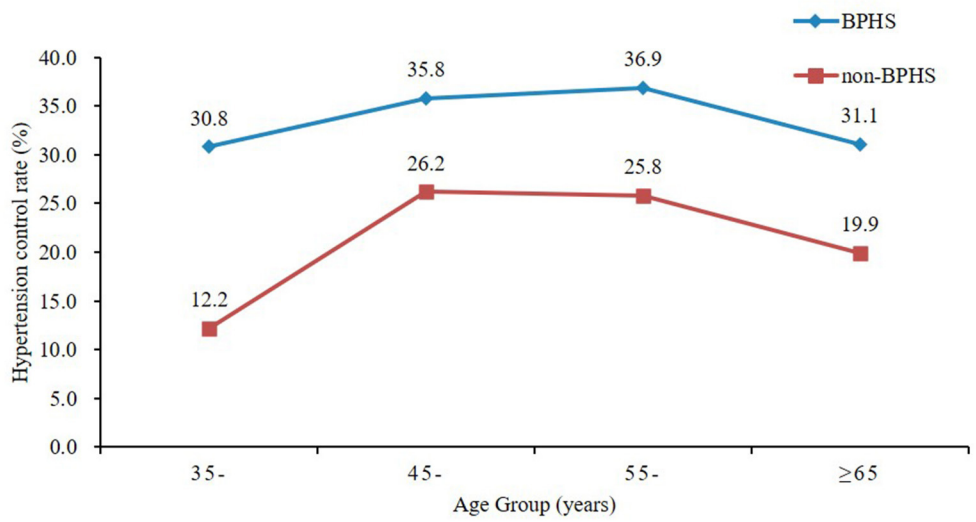

FIGURE 4
Hypertension control rate by age between the BPHS and non-BPHS groups.

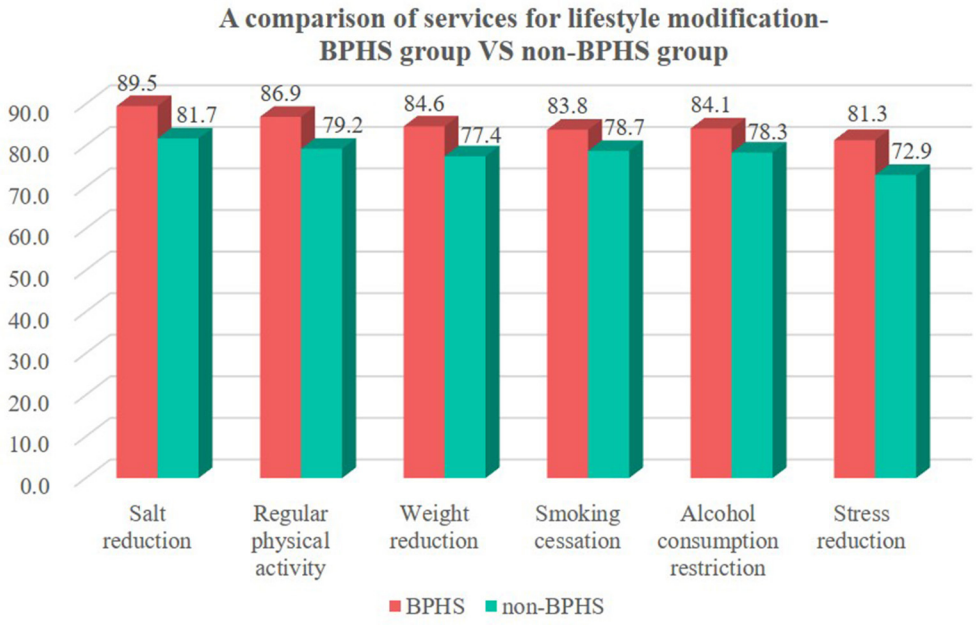

FIGURE 5
Hypertension patients received lifestyle modification services among BPHS and non-BPHS groups in Yunnan China.

lost in 1.7 million Chinese adults (39). Therefore, it is dire and imperative to ensure widespread BPHS accessibility and coverage. In addition, hypertensive patients have multiple risk factors (27, 40), and multiple cardiovascular disease risk factors will proportionately increase the risk of coronary artery, cerebrovascular, and renal disease (27, 29). An important part of BPHS is to assist with interventions of modifiable risk factors for hypertensive patients, including salt reduction, regular physical activity, weight reduction, smoking cessation, alcohol restriction, and reduction of psychological stress, consistent with the global practice guidelines developed by ISH (27), American College of Cardiology (41) and with the support of

TABLE 3 Differences in blood lipid measurements among patients included in the BPHS group.

Lifestyle modifications	TG	TC	LDL-C	HDL-C
Salt reduction				
YES	1.38 (0.93–2.24)	4.97 (4.26–5.65)	3.00 (2.44–3.60)	1.36 (1.17–1.58)
NO	1.50 (1.05–2.20)	5.20 (4.43–5.74)	3.10 (2.52–3.67)	1.43 (1.22–1.63)
p-Value	0.277	0.072	0.254	0.059
Regular physical activity				
YES	1.50 (1.03–2.19)	4.98 (4.28–5.66)	3.00 (2.45–3.60)	1.36 (1.17–1.58)
NO	1.47 (1.02–2.36)	5.18 (4.31–5.65)	3.05 (2.42–3.64)	1.41 (1.20–1.63)
p-Value	0.974	0.290	0.629	0.129
Weight reduction				
YES	1.49 (1.03–2.20)	4.93 (4.25–5.63)	2.98 (2.43–3.56)	1.36 (1.16–1.57)
NO	1.50 (1.04–2.36)	5.18 (4.50–5.77)	3.13 (2.52–3.67)	1.43 (1.23–1.65)
p-Value	0.832	0.011	0.079	0.009
Smoking cessation				
YES	1.49 (1.02–2.16)	4.93 (4.23–5.62)	2.99 (2.42–3.56)	1.36 (1.16–1.57)
NO	1.52 (1.05–2.59)	5.19 (4.47–5.89)	3.05 (2.51–3.66)	1.43 (1.21–1.62)
p-Value	0.251	0.008	0.121	0.022
Alcohol consumption restriction				
YES	1.49 (1.02–2.17)	4.93 (4.25–5.63)	3.00 (2.42−−3.58)	1.35 (1.16–1.57)
NO	1.52 (1.04–2.57)	5.21 (4.51–5.76)	3.11 (2.54–3.67)	1.43 (1.22–1.62)
p-Value	0.259	0.004	0.068	0.012
Stress reduction				
YES	1.49 (1.03–2.19)	4.95 (4.26–5.66)	3.00 (2.44–3.60)	1.35 (1.16–1.57)
NO	1.50 (1.04–2.37)	5.09 (4.31–5.65)	3.00 (2.44–3.60)	1.43 (1.20–1.64)
p-Value	0.607	0.381	0.600	0.025

Data was presented in Median (interquartile range), the differences between two groups were compared by Wilcoxon rank sum test.
BPHS, basic public health services; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

TABLE 4 Number of antihypertensive medications used and hypertension control rate between the BPHS and non-BPHS groups.

Number of drugs	Proportion			Control rate of hypertension		
	BPHS group	non-BPHS group	*p*-Value	BPHS group	non-BPHS group	*p*-Value
0 (Not taking medicine)	287 (28.4)	276 (54.1)	<0.001	75 (26.1)	27 (9.8)	<0.001
1	549 (54.3)	190 (37.3)	<0.001	189 (34.4)	66 (34.7)	0.853
2	151 (14.9)	41 (8.0)	<0.001	63 (41.7)	19 (39.0)	0.596
≥3	24 (2.4)	3 (0.6)	<0.001	9 (37.5)	0 (0.0)	0.529 #

Fisher's exact test.

extensive research evidence done on hypertension (8, 42–46). We also found hypertensive patients in the BPHS group had lower rates of smoking and drinking. Furthermore, as one of the indicators of the level of cardiovascular risk (29), patients included in BPHS management were beneficial in reducing TC after receiving lifestyle modification services. In comparison, the BPHS group had greater percentages of overweight and obese people, smokers, alcoholics, insufficient exercisers, and insufficient consumers of vegetables and fruits. All these are attributable to high lipids. At the same time, challenges remained as 42% of doctors in China's township health centers have only a college degree or less in 2018 (39). The average village clinic in Yunnan Province has two doctors who are required to provide daily consultation services and regular primary health care services for villagers, including the management of 180 hypertensive patients (7). These primary health care providers were faced with a heavy workload and had to compromise on quality in order to meet the quotas set by provincial Basic Public Health Services (18). Even though BPHS improved the service results, it still could not keep up with the fluctuating

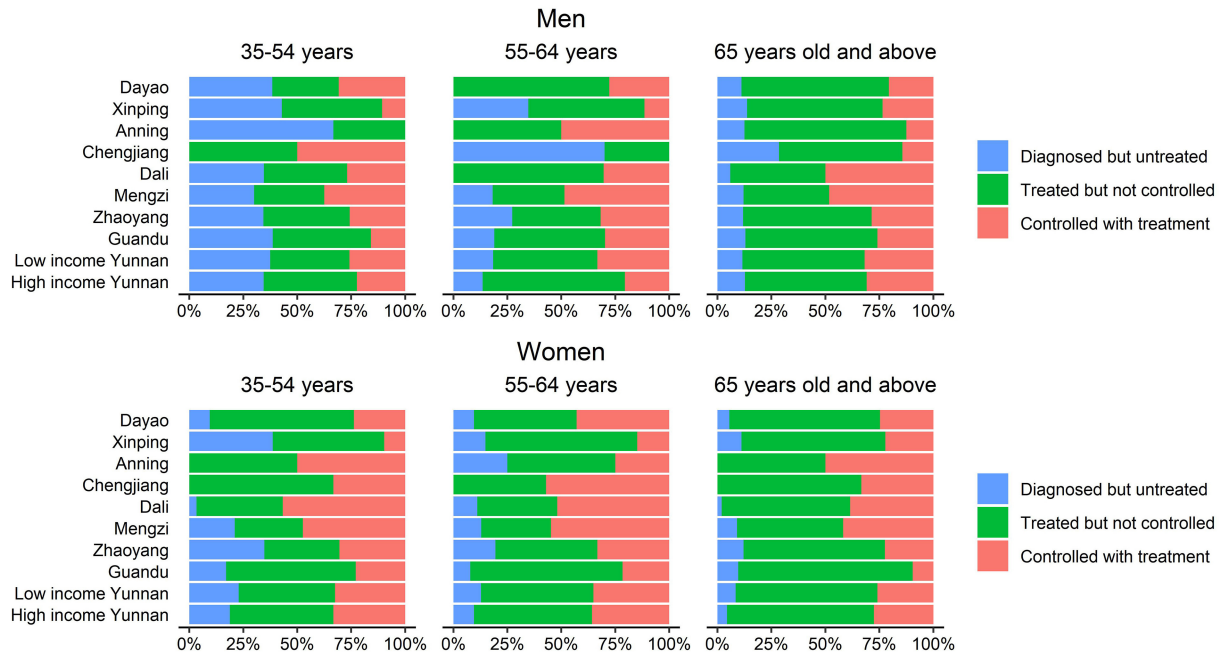

FIGURE 6
Distribution of blood pressure management status of hypertensive patients in Yunnan.

demand (18). The promotion of lifestyle modifications among high-risk populations under the guidance of BPHS in Yunnan Province has to be further enhanced, undoubtedly.

The study also found, in the BPHS group, 71.6% of hypertensive patients used antihypertensive medication (vs. non-BPHS 45.9%), which was higher than the national treatment rate of 61.3% (12). It may be related to the fact that the BPHS system in Yunnan Province has linked multiple medical electronic databases, benefiting from the management of more patients. Such patients receiving more BPHS accessible health education services, a better awareness of their health, and improved medication adherence, similar to the study in Zhejiang Province and Jiangsu Province in China (25, 47). Moreover, 17.3% of the BPHS patients used a combination of antihypertension drugs (vs. non-BPHS 8.6%), which has facilitated blood pressure control to normal in patients in the BPHS group. However, there is still room for improvement in the BPHS, as evidenced by the fact that in Yunnan Province especially in rural districts, only 39% of antihypertensive drug users had visited a doctor or taken medication in the previous 3 months (48).

Generally, the control rate of hypertension is the standard for evaluating the effectiveness of interventions, resulting in effectively preventing or delaying the occurrence of stroke, myocardial infarction, heart failure, renal insufficiency, and other complications (29). Our study revealed that the BPHS group had a significantly higher control rate, and the multivariate regression analysis found the BPHS group has a 4.8 times more likely chance of having a high blood pressure control rate than the non-BPHS group (OR = 1.640, 95% CI: 1.237–2.175). Moreover, in comparison with hypertensive patients in the non-BPHS group, the hypertension control rate for all ages among those who received BPHS management was significantly higher. Those who participated in BPHS management (26.1%) had a higher control rate than those who did not include in BPHS management (9.8%) despite untreated with hypertension medication, which may be explained by the blood pressure monitoring, risk factor intervention and referral services provided by primary care physicians in BPHS. The results also supported earlier studies indicating that in Yunnan province, women were more aware of and controlled their hypertension than men (48). Besides, hypertensive patients under 65 more unlikely being managed by BPHS in rural areas. It suggests the importance of early screening of younger patients and makes BPHS more capable of providing for the concerns of the younger population to control the morbidity of hypertension at a very early stage. The fact that more than half of our subjects had completed middle school or less and 76.3% of them had household incomes of <USD 4487/year illustrated the validity of the BPHS, the critical role it plays in early screening, prevention and control of hypertension in areas with limited resources, and the ability to share the experience with other developing nations.

Limitations include the design method in this survey, this might not substantiate causation, particularly the link between

the services offered by the BPHS program and the management of hypertension without these services. Recall bias can also be a challenge with self-reported data. Some subjects lacked information, such as height or weight, which can skew the data. Therefore, information collection and interpretation of risk factor changes should be conducted with utmost care.

Conclusions

Since its launch in 2009, the BPHS program run by provincial authority healthcare providers has made a substantial contribution to bettering hypertension management and balancing access to healthcare across inhabitants of urban and rural areas as well as among various socioeconomic strata.

Results showed that program participants kept healthy lifestyles, had lower blood pressure, higher control rate of hypertension, and took their medications more consistently, which could account for some of the benefits of this program. In districts or counties with fully operational digitalized and centralized data management systems, it was easier to include the participants compared to "non-matched ID" in rural areas, therefore health information management may further be improved to address this limitation in rural areas. In order to better diagnose and treat hypertension at its early stages, a customized program has to be designed to cater to the requirements of hypertension control in the younger population through the BPHS program.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the central Ethics Committee at the Fuwai Hospital, CAMS/National Center for Cardiovascular Diseases approved this project (approval no. 2020–1360, approval date: August 11, 2020). The survey was conducted in accordance with the ethical principles of the Declaration of Helsinki, and the informed consent and electronic signature of the participants were obtained before the investigation. The patients/participants provided their written informed consent to participate in this study.

Author contributions

LP and LK were co-first authors and drafted the manuscript. ZG and YZ initiated, conceived, and supervised the study. LD, WL, and MF guided the analysis and modified the article. LP, JF, and HF were involved in data curation and analysis. YS and MT completed field execution and coordinated all divisions. XW, MM, and HW checked the integrity of the data. LK and DM reviewed and edited the manuscript. LD conceptualized and supervised this project. All authors have read and approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1017795/full#supplementary-material

SUPPLEMENTARY FILE 1
Questionnaires.

SUPPLEMENTARY FILE 2
Visual abstract - Summary of the investigation process of this study.

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Effect of exercise on vascular function in hypertension patients: A meta-analysis of randomized controlled trials

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Objective: The purpose of this study was to systematically evaluate the effect of exercise on vascular function in patients with pre- and hypertension.

Methods: A systematic review of articles retrieved *via* the PubMed, Embase, EBSCO, and Web of Science databases was conducted. All the randomized controlled trials published between the establishment of the databases and October 2022 were included. Studies that evaluated the effects of exercise intervention on vascular function in patients with pre- and hypertension were selected.

Results: A total of 717 subjects were included in 12 randomized controlled trials. The meta-analysis showed that in patients with pre- and hypertension, exercise can significantly reduce systolic blood pressure (SBP) (*MD* = −4.89; 95% CI, −7.05 to −2.73; $P < 0.00001$) and diastolic blood pressure (DBP) (*MD* = −3.74; 95% CI, −5.18 to −2.29; $P < 0.00001$) and can improve endothelium-dependent flow-mediated dilatation (*MD* = 2.14; 95% CI, 1.71–2.61; $P < 0.00001$), and exercise did not reduce pulse wave velocity (PWV) (*MD* = 0.03, 95% CI, −0.45–0.50; $P = 0.92$). Regression analysis showed that changes in exercise-related vascular function were independent of subject medication status, baseline SBP, age and duration of intervention.

Conclusion: Aerobic, resistance, and high-intensity intermittent exercise all significantly improved SBP, DBP, and FMD in pre- and hypertensive patients, however, they were not effective in reducing PWV, and this effect was

independent of the subject's medication status, baseline SBP, age and duration of intervention.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/, identifier CRD42022302646.

KEYWORDS

exercise, hypertension, vascular, meta-analysis, review

Introduction

As is well-known, hypertension, as a chronic disease, is one of the main risk factors for cardiovascular diseases. According to the World Health Organization (WHO), one billion people suffer from hypertension worldwide, and about nine million people currently die each year due to elevated blood pressure (1). The 2017 American College of Cardiology (ACC)/American Heart Association (AHA) blood pressure guidelines suggest that the cutoff point for hypertension diagnosis is systolic blood pressure (SBP) > 130 mm Hg or diastolic blood pressure (DBP) > 80 mm Hg (2). Available evidence suggests that cardiovascular prevalence is significantly higher in pre-hypertensive and hypertensive subjects than in healthy adults (3). Hypertension is highly linearly correlated with cardiovascular and cerebrovascular disease (CVD) and all-cause mortality (ACM), and blood pressure values have a linear relationship with the incidence of cardiovascular and CVDs; every 20 mm Hg increase in SBP or 10 mmHg increase in DBP doubled the risk of cardiovascular disease (4).

Elevated blood pressure can destroy vascular structure and function and the autocrine–paracrine relationship of the vascular wall (5). Hypertension is characterized by endothelial dysfunction and arterial remodeling, which lead to increased vascular wall thickness and arterial stiffness, which in turn increase blood pressure, forming a vicious cycle (6–9). SBP, DBP, FMD [Flow-mediated dilation (FMD)], and PWV (Pulse wave velocity) are correlated with the incidence of hypertension (2, 4, 5, 10–13). Vascular endothelium plays an important role in regulating angiogenesis, inflammatory response, angiogenesis, and peripheral vascular resistance (14). Endothelium-dependent FMD is one of the indicators of endothelial function and an increase in FMD is associated with improved cardiovascular disease, with studies showing that a 1% increase in FMD is associated with a 13% reduction in cardiovascular risk (15). High blood pressure will disorder vascular endothelial cells and consequently lead to decreased FMD (8). Arterial stiffness is a risk factor for hypertension. PWV refers to the conduction velocity of the pressure wave propagating along the wall of the aorta with each pulse ejection, and it is a non-invasive index for evaluating the stiffness of arterial vessels, and PWV measurements are considered more sensitive than conventional blood pressure measurements (16). Theoretically, increased arterial stiffness is related to the loss of arterial elasticity and decreased compliance, and increased blood pressure will lead to vascular wall remodeling and vascular dysfunction, in order to compensate for changes in vascular wall stress, thus further aggravating arterial stiffness (17). Therefore, improving vascular function is essential for management and prevention strategies in patients with pre-hypertension and hypertension.

A large number of experimental and observational studies have demonstrated that lifestyle-based interventions, such as increased physical activity and dietary approaches, are effective in preventing CVD (18–20). Exercise, as a non-drug treatment, can effectively decrease hypertension. Studies have shown that regular exercise can improve cardiovascular health and reduce blood pressure; among many forms of exercise, aerobic exercise (AE) has become the primary recommendation for the prevention and treatment of hypertension (21–23). The lifestyle-management guidelines published by the ACC and AHA suggest that patients with cardiovascular diseases such as hypertension should perform 40 min of moderate-intensity AE three to four times per week for at least 12 weeks (24). Studies have demonstrated that regular AE can reduce the impairment of endothelium-dependent vasodilation (25) and atherosclerosis (26) in patients with hypertension. Unlike the research on AE, the research on resistance training (RT) is controversial. The AHA (27), American College of Sports Medicine (ACSM) (28), European Society of Hypertension (ESH/ESC) (29), and Canadian Hypertensive Education Program (CHEP) (30) recommend RT only as a supplement to AE in adults with hypertension. Other studies have shown that RT reduces blood pressure in adult hypertensive patients and that this reduction may be similar to that associated with AE (31, 32). Although RT can effectively reduce blood pressure, its ability to improve vascular endothelial function and vascular stiffness in patients with hypertension is debated. Two recent studies have shown that high-intensity resistance exercise reduces FMD and increases arterial stiffness (33, 34), while others have demonstrated that resistance exercise does not

affect the increase or decrease in PWV (35). Few studies have investigated the effect of high-intensity interval training (HIIT) on vascular function in hypertensive patients. Some studies have shown that, compared with AE, HIIT can more effectively improve blood pressure, endothelial function (36) and arterial stiffness (37). Although research has shown that exercise reduces hypertension, few studies have focused on the effects of exercise on vascular function in patients with hypertension, and it is not clear which mode of exercise (AE, RT, or HIIT) has the best effect on vascular function in such patients. Therefore, in this study, we investigated the different effects of exercise on endothelial function and arterial stiffness in pre- and hypertensive patients based on the fact that exercise can lower blood pressure and to provide most suitable exercise advice for preventing vascular pathology in patients with hypertension.

Methods

The writing of this article strictly followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (38).

Data sources and searches

In this study, two experienced researchers conducted a literature search in PubMed, Embase, EBSCO, Web of Science, and other databases. The retrieval time was from the establishment of the database to October 2022, and the references included in the literature were tracked. The search terms were as follows: exercises OR physical activity OR isometric exercises OR AE OR exercise training AND vascular endothelium OR capillary endothelium OR endothelium, capillary AND vascular OR blood vessels OR vessel, blood OR vessels, blood.

Study selection

Studies were eligible for inclusion if they met all the following criteria: (1) experimental type: RCT, (2) subjects: patients with hypertension or prehypertension, (3) intervention: the experimental group exercised and the control group did not exercise and the exercise duration of the experimental group was more than 4 weeks, and (4) outcome indicators: SBP, DBP, FMD, PWV. Studies were excluded if (1) they lacked an RCT, (2) they lacked a blank control group, (3) repeated studies, (4) they provided no outcome indicators, (5) accompanied by myocardial infarction, chronic heart failure, arrhythmia and other cardiovascular diseases, (6) they were reviews or conference reports, (7) they contained animal experiments, or (8) they were written in a language other than English.

Data screening and extraction

According to the retrieval strategy, all the retrieved studies were imported into the literature-management software EndNote and duplicate studies were deleted. Two of the researchers screened the literature according to the inclusion and exclusion criteria. The determination to exclude a study was made by reading the title and abstract, downloading the full text of the study, and reading the full text in detail. The two researchers compared their screening results. If the screening results were inconsistent, a third researcher was enlisted to discuss the decision. In case of incomplete data or unclear description of the finally included literature, the author of the literature shall be contacted by e-mail. The outcome indicators were extracted from the studies that were ultimately included, and the tables were designed and completed by the two researchers independently. The extracted content consisted of (1) basic information about the included studies: first author, publication date, etc., (2) the subjects' baseline characteristics: age, sex, medication status and blood pressure, (3) the intervention measures applied to the experimental group: exercise duration, exercise mode, and exercise intensity, and (4) the relevant outcome indicators and outcome data.

Quality assessment

Using the Cochrane Collaboration's tool for assessing the risk of bias (39), the included studies were evaluated for seven aspects of methodological quality, as follows: (1) random sequence generation, (2) allocation hidden, (3) blind method for subjects and experimentalists, (4) blinding of outcome assessment, (5) incomplete data report, (6) the results of selective reporting, and (7) other sources of bias.

Statistical analysis

In this study, the included literature data were uniformly converted to mean ± standard deviation (M ± SD). RevMan 5.3 and STATA 12.0 software provided by the Cochrane Library Collaboration network (StataCorp., College Station, Texas, USA) the difference of mean ± standard deviation (M ± SD) before and after intervention was analyzed. The heterogeneity of the included data was assessed by calculating the value of I^2. The Cochran Handbook suggests that if $I^2 < 50\%$ and Q-test $P > 0.1$, the heterogeneity among different study groups is small; if this was the case, a fixed effects model was adopted for analysis. If $I^2 \geq 50\%$ or Q-test $P \leq 0.1$, both of which indicate a high level of heterogeneity among the study groups, a random effects model was adopted. SBP, DBP, FMD, and PWV outcomes were continuous variables, and the measurement units were the same. Therefore, a mean difference

(MD) effect scale and a 95% confidence interval (CI) were used for the statistics. Subgroup analysis and sensitivity analysis were carried out according to the results of possible sources of heterogeneity, and a publication-bias test was carried out. Egger's method was used for quantitative testing. If $P < 0.05$, there was publication bias, and this bias was eliminated using the cut-and-complement method.

Results

Literature search and selection

According to the established literature retrieval strategy, a total of 1,779 articles were retrieved. The databases used and the number of articles detected by each database are as follows: PubMed ($n = 594$), EMBASE ($n = 259$), Web of Science ($n = 827$), EBSCO ($n = 99$). The literature-management software EndNote was used to eliminate 203 duplicate articles, and 1,510 articles were deleted after reading their titles and abstracts. After the full text of the articles was read, 54 articles were removed and 12 were ultimately included, as shown in **Figure 1**.

Description of the included trials

Based on the 12 included studies, a total of 717 subjects (469 in the exercise group and 248 in the control group) were included. Among these studies, one article included postmenopausal women (40, 41), one included type 2 diabetes mellitus (T2DM) (42), and two included metabolic syndrome (12, 43). Four of the studies used two exercise programs (37, 42–44), two used three exercise programs (12, 40), four used an RT intervention (10, 12, 41, 44), 8 used an AE intervention (37, 40, 42–47), and five used a HIIT intervention (11, 12, 37, 42, 43). The members of the control group did not perform an exercise intervention and maintained their previous lifestyle. One intervention lasted 6 weeks (41), one lasted 8 weeks (44), four lasted 12 weeks (42, 45–47), two lasted 16 weeks (37, 43),

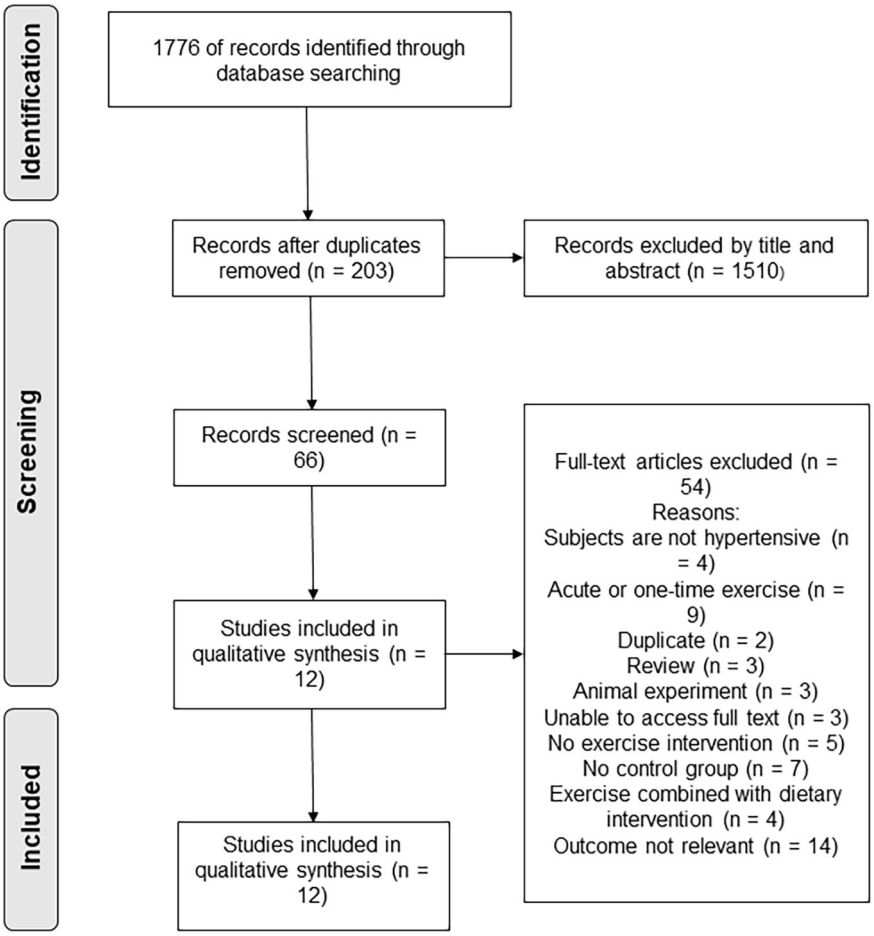

FIGURE 1
Flowchart of the literature-retrieval protocol.

and two lasted 24 weeks (11, 40). Nine studies reported an exercise frequency of 3 days/week (10–12, 37, 42–46), one reported an exercise frequency of 3–4 days/week (40), one reported an exercise frequency of 5 days/week (46), and one reported an exercise frequency of 6 days/week (41). There were 7 studies in which subjects took anti-hypertensive medicines, and 5 studies in which subjects did not take anti-hypertensive medicines (**Table 1**).

Methodological quality assessment

The included articles were evaluated for risk bias. Five of the 12 included studies mentioned the use of random grouping and involved random sequence generation. Allocation hiding was achieved in one study, whereas random sequence generation was achieved in the other studies. Two studies involved blinding of participants and personnel, whereas the other studies failed to achieve blinding of participants and personnel. Blinding of outcome assessment was performed in one study but not in the others. Incomplete outcome data attrition bias was achieved in 12 studies. Selective reporting was used in 12 studies. Twelve studies determined that no other bias existed (**Figure 2**).

Synthesis of the results

Analysis of systolic blood pressure

A pooled analysis of the 12 articles (n = 717 participants, 469 in the exercise group and 248 in the control group) that assessed the effects of exercise on SBP was performed. We used random effects models for pooled effect estimates. The combined effect size MD of −4.89 (95% CI, −7.05 to −2.73; $P < 0.00001$; I^2 = 85%; P for heterogeneity < 0.00001) indicated that the MD of SBP was statistically significant and that, compared with the control group, exercise could significantly decrease the SBP of pre- and hypertensive patients. The subgroup analysis showed that 10 studies (n = 531) used AE with a combined effect MD of −3.51 (95% CI, −5.85 to −1.17; P = 0.003; I^2 = 86%; P for heterogeneity < 0.00001), suggesting that AE can significantly decrease SBP in pre- and hypertensive patients. Four studies (n = 112) used RT with a combined effect MD of −10.39 (95% CI, −12.64 to −8.15; $P < 0.00001$; I^2 = 0%; P for heterogeneity = 0.80), suggesting that RT can significantly decrease SBP in pre- and hypertensive patients. Five studies (n = 162) used HIIT with a combined effect MD of −4.23 (95% CI, −8.07 to −0.38; P = 0.007; I^2 = 32%; P for heterogeneity = 0.21), suggesting that HIIT can significantly decrease SBP in pre- and hypertensive patients. One study (n = 21) used combination exercise with a combined effect MD of −3.40 (95% CI, −19.12 to 12.32; P = 0.67), suggesting that there was no statistically significant difference in SBP between the two groups (**Figure 3**).

Analysis of diastolic blood pressure

A pooled analysis of the 12 articles (n = 717 participants, 469 in the exercise group and 248 in the control group) that assessed the effects of exercise on DBP was performed. We used random effects models for pooled effect estimates. The combined effect size MD of −3.74 mmHg (95% CI, −5.18 mmHg to −2.29 mmHg; $P < 0.00001$; I^2 = 87%; P for heterogeneity < 0.00001) indicated that the MD of DBP was statistically significant and that, compared with the control group, exercise could significantly improve the DBP of pre- and hypertensive patients. The subgroup analysis showed that 10 studies (n = 531) used AE with a combined effect MD of −2.77 mmHg (95% CI, −4.22 mm Hg to −1.32 mm Hg; P = 0.0002; I^2 = 83%; P for heterogeneity < 0.00001), suggesting that AE can significantly decrease DBP in pre- and hypertensive patients. Four studies (n = 112) used RT with a combined effect MD.

Of −5.67 mm Hg (95% CI, −8.82 to −2.52 mm Hg; P = 0.0004; I^2 = 54%; P for heterogeneity = 0.09), suggesting that RT can significantly decrease SBP in pre- and hypertensive patients. Five studies (n = 162) used HIIT with a combined effect MD of −4.57 mm Hg (95% CI, −6.46 to −2.69 mm Hg; $P < 0.00001$; I^2 = 10%; P for heterogeneity = 0.35), indicating that HIIT can significantly decrease DBP in pre- and hypertensive patients. One study (n = 21) used combination exercise with a combined effect MD of 1.40 mm Hg (95% CI, −6.73 to 9.53 mm Hg; P = 0.74), suggesting that there was no statistically significant difference in DBP between the two groups (**Figure 4**).

Analysis of flow-mediated dilation

A pooled analysis of the nine articles (n = 571 participants, 378 in the exercise group and 193 in the control group) that assessed the effects of exercise on FMD was performed. We used random effects models for pooled effect estimates. The combined effect size MD was 2.14 (95% CI, 1.71–2.61; $P < 0.0001$; I^2 = 81%; P for heterogeneity < 0.00001), indicating that the MD of FMD was statistically significant and that, compared with the control group, exercise could significantly improve the FMD of patients. Subgroup analysis showed that seven studies (n = 446) used AE, with a combined effect MD of 1.92 (95% CI, 1.44–2.41; $P < 0.00001$; I^2 = 79%; P for heterogeneity < 0.00001), suggesting that AE can significantly improve FMD in patients. Three studies (n = 79) used RT, with a combined effect MD of 2.61 (95% CI, 1.91–3.31; $P < 0.00001$; I^2 = 0%; P for heterogeneity = 0.99), suggesting that RT can significantly improve FMD in patients. Three studies (n = 77) used HIIT with a combined effect MD of 4.31 (95% CI, 0.78–7.84; P = 0.02; I^2 = 94%; P for heterogeneity < 0.00001), indicating that HIIT can significantly improve FMD in patients. One study (n = 21) used combination exercise with a combined effect MD of 1.56 (95% CI, 0.99–2.13; $P < 0.00001$), indicating that combination exercise can significantly improve FMD in patients (**Figure 5**).

TABLE 1 Characteristics of the included trials.

Study	Patients	Medication status	Control		Exercise		Intervening measure and intensity	Intervention duration	Outcome indicator
			Sample size (M/F)	Age	Sample size (M/F)	Age			
Afousi et al. (42)	T2DM, SBP: 120–159 mm Hg, DBP: 80–99 mm Hg	aHTN	17 (8/9)	54.24 ± 5.61	LVHIIT: 18 (9/9)	54.78 ± 6.19	LVHIIT, 85–90% HR_{max}, 2 min at 55–60% HR_{max}, 1.5 min, 12 intervals	3 d/w, 12 w	SBP, DBP, FMD
					CMIT: 17 (7/10)	53.12 ± 4.84	AE (CMIT), 40% HR_{max}, 42 min		
Craighead et al. (41)	SBP: 120–139 mm Hg, DBP: 80–89 mm Hg	aHTN	18 (10/8)	67 ± 2	18 (9/9)	67 ± 2	Week 1: 55% PIMAX, week 2: 65% PIMAX, week 3: 67.5% PIMAX	6 d/w, 6 w	SBP, DBP, FMD, PWV
Glodzik et al. (45)	SBP: 131.65 ± 3.57 mm Hg, DBP: 80.65 ± 5.21 mm Hg	None	14 (8/6)	45.0 ± 3.41	31 (23/8)	44.3 ± 5.57	AE, 40–65% HRR	3 d/w, 12 w	SBP, DBP, FMD
Liang et al. (46)	SBP: 140–159 mm Hg, DBP: 90–99mm Hg	None	66 (66/0)	18–40	75 (75/0)	18–40	AE, 75% maximal metabolic equivalent	5 d/w, 12 w	SBP, DBP, FMD, PWV
Westhoff et al. (47)	SBP ≥ 140 mm Hg	aHTN	12 (5/7)	68.4 ± 9.7	12 (6/6)	66.1 ± 4.0	AE (aerobic arm cycling), target lactate concentrations of 2.0∼0.5 mmol/L	3 d/w, 12 w	SBP, DBP, FMD
Guimarães et al. (37)	SBP: 120–139 mm Hg, DBP:80–89 mm Hg	aHTN	11 (9/2)	47 ± 6	Continuous: 16 (9/7)	50 ± 8	AE, 60% HRR	40 min/d, 3 d/w, 16 w	SBP, DBP, PWV
					Interval: 16 (12/4)	45 ± 9	HIIT, 50% (2 min) and 80% (1 min) HRR		
Beck (44)	SBP: 120–139 mm Hg, DBP:80–89 mm Hg	None	15 (10/5)	21.6 ± 2.9	PHET: 13 (9/4)	20.1 ± 1.1	PHET, AE, 65 –85% HR_{max}	60 min/d, 3 d/w, 8 w	SBP, DBP, FMD
					PHRT: 15 (11/4)	21.1 ± 2.5	PHRT, 8–12 RM		
Swift et al. (40)	Postmenopausal, SBP: 120–159 mm Hg, overweight	None	23 (0/23)	56.8 ± 5.4	4 kcal/kg/week: 68 (0/68)	57.4 ± 5.8	AE, 50% VO_2 peak	3 or 4 d/w, 24 w	SBP, DBP, FMD
					8 kcal/kg/week: 32 (0/32)	55.9 ± 6.0			
					12 kcal/kg/week: 32 (0/32)	56.3 ± 6.8			
Cahu Rodrigues et al. (10)	SBP: 120–139 mm Hg, DBP:80–89 mm Hg	aHTN	17	59 ± 2	16	61 ± 2	RT (isometric handgrip training), 30% of maximal voluntary contraction	3 d/w, 12 w	SBP, DBP, PWV
Mora-Rodriguez et al. (11)	SBP ≥ 130 mm Hg and/or DBP ≥ 85 mm Hg	None	23	53.5 ± 8.9	23	53.5 ± 8.9	HIIT, 4 min 90% HR_{max}, 3-min recovery at 70% HRmax, 4 intervals	45 min/d, 3 d/w, 24 w	SBP, DBP, PWV
Stensvold et al. (12)	SBP ≥ 130 mm Hg and/or DBP ≥ 85 mm Hg, syndrome	OHG, aHTN	11	47.3 ± 10.2	AIT:11	49.9 ± 10.1	AIT, 4 min at 90–95% of HR_{peak}, 3-min recovery at 70% of HR_{peak}, 4 intervals		SBP, DBP, FMD
					RT:11	50.9 ± 7.6	RT, 80% 1-RM, 8–12 repetitions, 3 sets	3 d/w, 12 w	
					COM:10	52.9 ± 0.4	COM, AIT twice a week and RT once a week		

(Continued)

TABLE 1 Continued

Study	Patients	Medication status	Control		Exercise		Intervening measure and intensity	Intervention duration	Outcome indicator
			Sample size (M/F)	Age	Sample size (M/F)	Age			
Tjønna et al. (43)	SBP ≥ 130 mm Hg and/or DBP ≥ 85 mm Hg, syndrome	OHG, aHTN	9 (5/4)	49.6 ± 9.0	CMIT:8 (4/4) AIT:11 (4/7)	52.0 ± 10.6 55.3 ± 13.2	CMIT, 70% HR_{max} AIT, 4-min 90% HR_{max}, 3-min 70% of HR_{max}, 4 intervals	3 d/w, 16w	SBP, DBP, FMD

aHTN, antihypertensive drugs; OHG, oral hypoglycemic agents; T2DM, Type 2 Diabetes Mellitus; M, male; F, female; HIIT, High Intensity Interval Training; CMIT, continuous moderate intensity training; PHET, endurance exercise training; PHRT, resistance exercise training; AIT, aerobic interval training; RT, resistant training; COM, combination of AIT and RT; AE, aerobic exercise; HRR, heart rate reserve; HRmax, maximal heart rate; HRpeak, peak heart rate; VO_2 peak, Peak oxygen uptake; PIMAX, maximal inspiratory pressure; RM, repetition maximum.

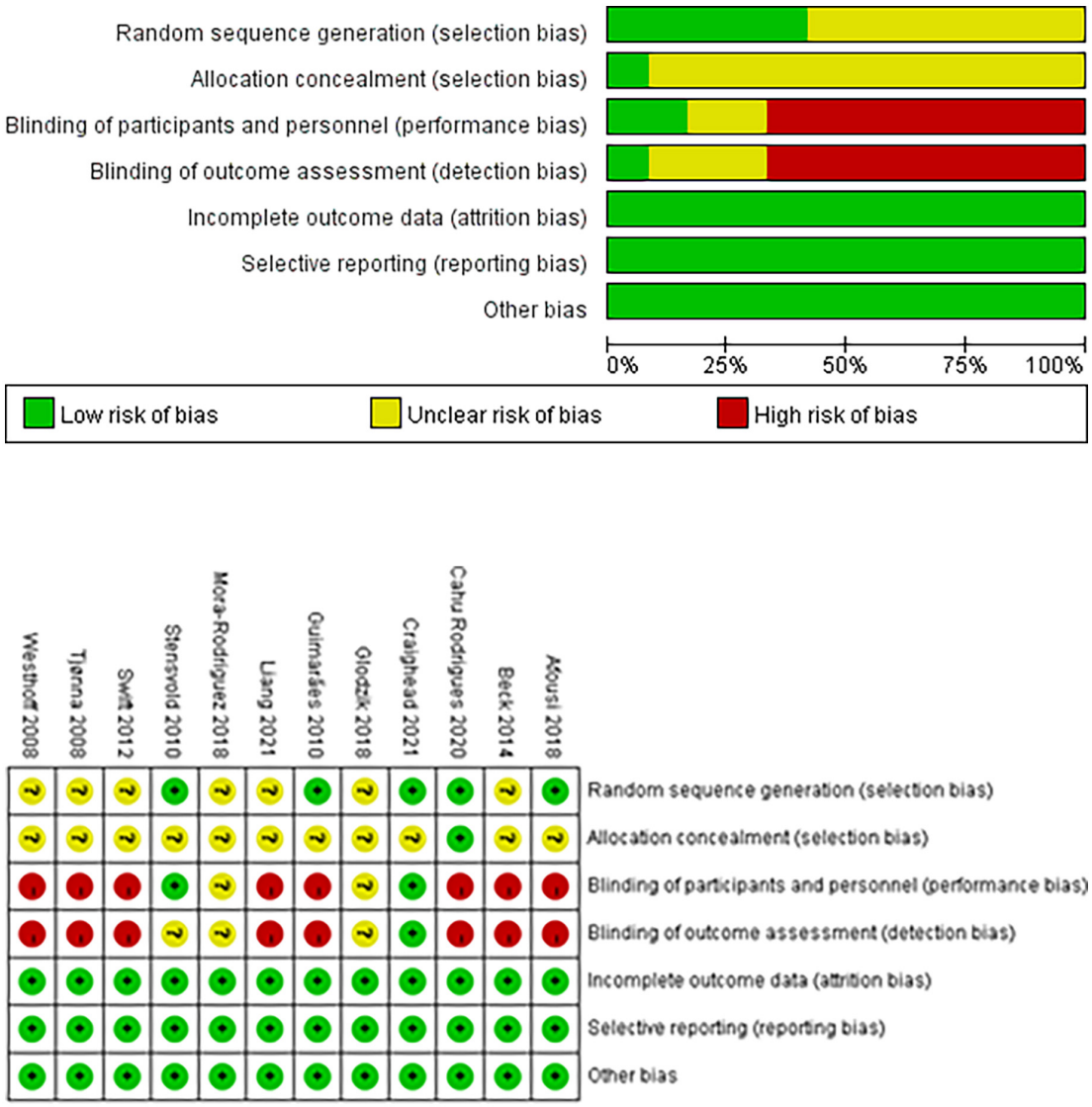

FIGURE 2
Cochrane risk-of-bias evaluation chart.

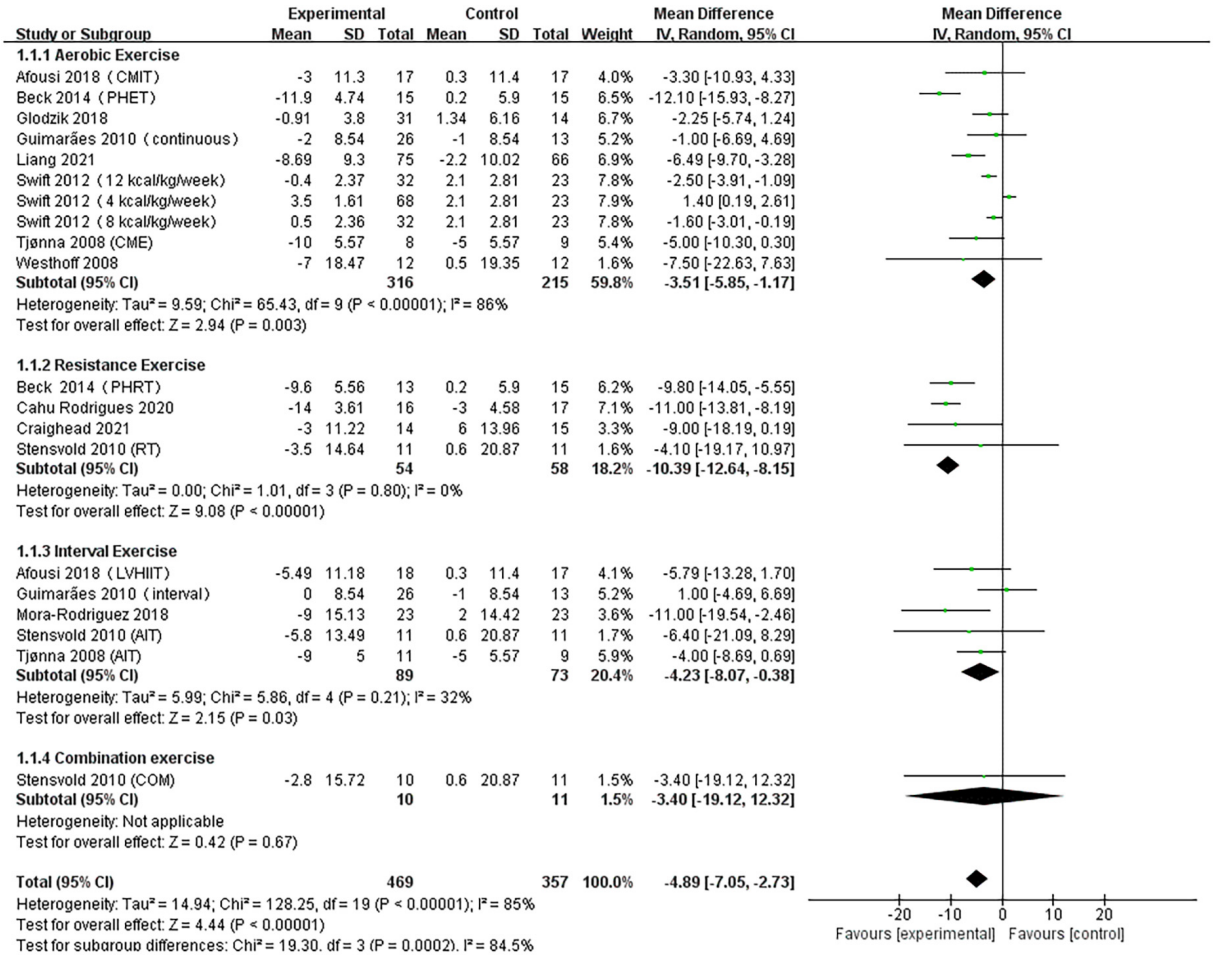

FIGURE 3
Forest plot of postintervention SBP-value comparison between exercise and control groups. SD, standard deviation; Std, standardized; IV, inverse variance; CI, confidence interval; CME, continuous moderate exercise; LVHIIT, low-volume high-intensity interval training.

Analysis of pulse wave velocity

A pooled analysis of the five articles (n = 314 participants, 180 in the exercise group and 134 in the control group) that assessed the effects of exercise on PWV was performed. We used random effects models for pooled effect estimates. The combined effect size MD of 0.03 (95% CI, −0.45 to 0.50; P = 0.92; I^2 = 54%; P for heterogeneity = 0.05) indicated that the MD of PWV was not statistically significant. The subgroup analysis showed that two studies (n = 180) used AE, with a combined effect MD of −0.46 (95% CI, −0.96 to 0.05; P = 0.08; I^2 = 0%; P for heterogeneity = 0.75), suggesting that there was no statistically significant difference in PWV between the two groups and that AE cannot significantly improve PWV in hypertensive patients. Two studies (n = 62) used RT with a combined effect MD of 0.19 (95% CI, −0.04 to 0.43; P = 0.11; I^2 = 0%; P for heterogeneity = 0.72), indicating that there was no statistically significant difference in PWV between the two groups. Two studies (n = 85) used HIIT, with a combined effect MD of 0.54 (95% CI, −1.32 to 2.40; P = 0.57, I^2 = 78%; P for heterogeneity = 0.03), indicating that there was no statistically significant difference in PWV between the two groups (**Figure 6**).

Meta-regression analysis

Univariate meta-regression analysis showed that changes in FMD and PWV associated with exercise were independent of the subjects' medication status, basal SBP, age and duration of exercise (**Table 2**). Further subgroup analysis of subjects included in the study showed that exercise significantly improved FMD in hypertensive patients taking (MD = 2.36, I^2 = 81%, P < 0.00001) or not taking (MD = 2.11, I^2 = 73%, P < 0.00001) antihypertensives, with a basal SBP ≥ 140 mm Hg (MD = 1.94, I^2 = 55%, P < 0.00001) or SBP < 140 mm

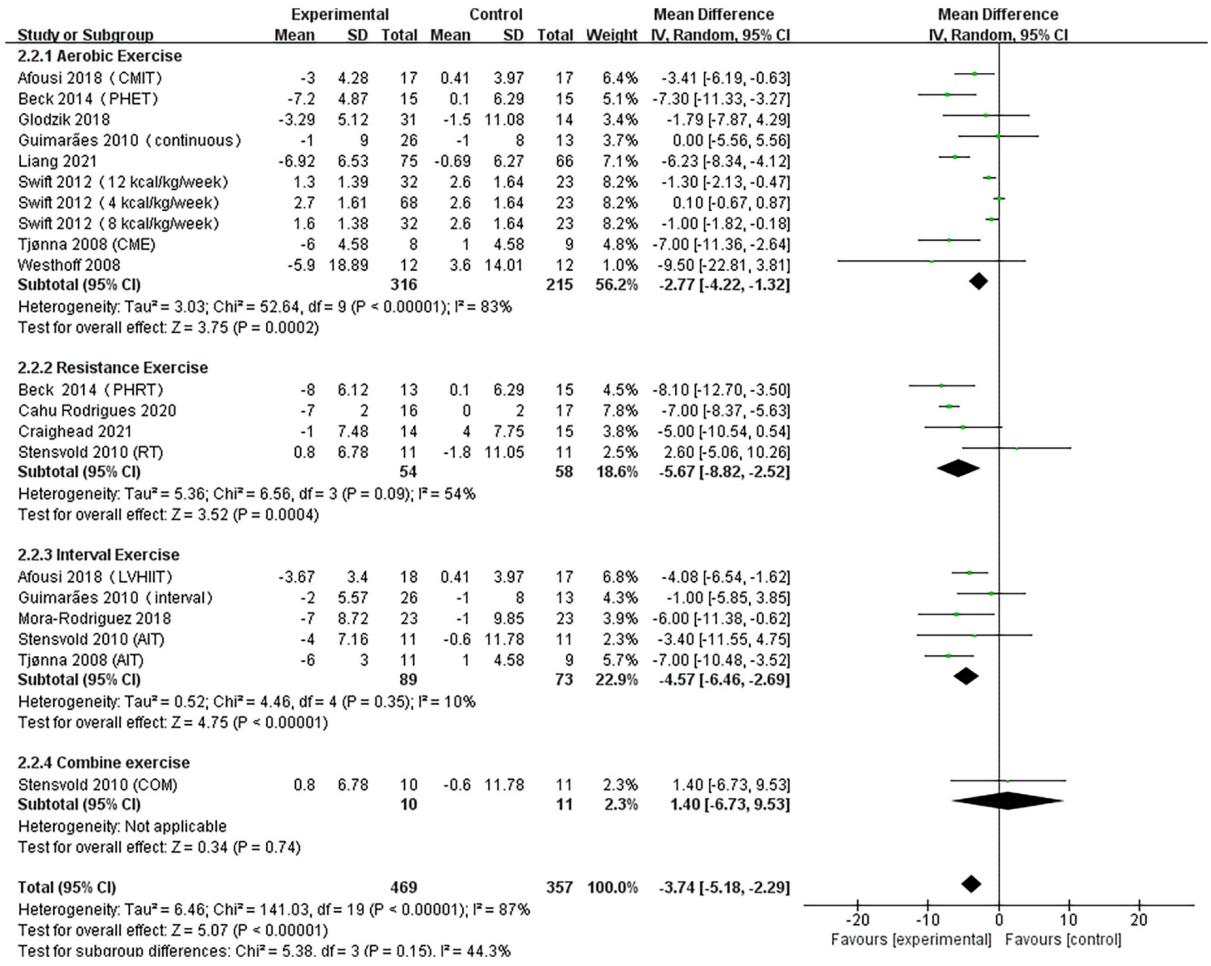

FIGURE 4
Forest plot of postintervention DBP-value comparison between exercise and control groups. SD, standard deviation; Std, standardized; IV, inverse variance; CI, confidence interval.

Hg (MD = 2.34, I^2 = 85%, P < 0.00001), and aged ≥ 50 (MD = 2.01, I^2 = 82%, P < 0.00001) or < 50 (MD = 2.81, I^2 = 80%, P < 0.00001) years, with similar effects. In contrast, there was no significant change in PWV after the exercise intervention in hypertensive subjects taking (MD = −0.17, I^2 = 88% P = 0.08) or not taking (MD = 2.36, I^2 = 81%, P < 0.00001) antihypertensives, with basal SBP ≥ 140 mm Hg (MD = −0.49, P = 0.08) or SBP < 140 mm Hg (MD = 0.20, I^2 = 29%, P = 0.42), aged ≥ 50 (MD = 0.27, I^2 = 42%, P = 0.38) or < 50 (MD = −0.46, I^2 = 0%, P = 0.08) years, and with exercise duration ≥ 12 weeks (MD = 0.04, I^2 = 63%, P = 0.89) or < 12 weeks (MD = −0.06, P = 0.93) (**Table 3**).

Sensitivity analysis

To test the stability and reliability of the meta-analysis results, the sensitivity of exercise to SBP, DBP, FMD, and PWV was analyzed. After the removal of each study, the results of the sensitivity analysis showed that the results were relatively robust, as shown in **Supplementary Figure 1**.

Evolution of publication bias

Stata version 12.0 was used for the publication bias test, a funnel diagram was made for SBP, DBP, FMD and PWV, and Egger's method was used for the quantitative test. The funnel diagram of exercise on SBP was asymmetric. Egger's test t = −2.35, P > 0.030, and there is publication bias test. We used the trim and fill method to eliminate the publication bias of exercise on SBP. After the trim and fill method was performed, the publication bias was eliminated, the combined effect amount did not change, and there was still a significant difference (MD = −4.890; 95% CI, −7.047 to −2.733; P = 0.000). The funnel diagram of exercise on DBP was asymmetric. Egger's

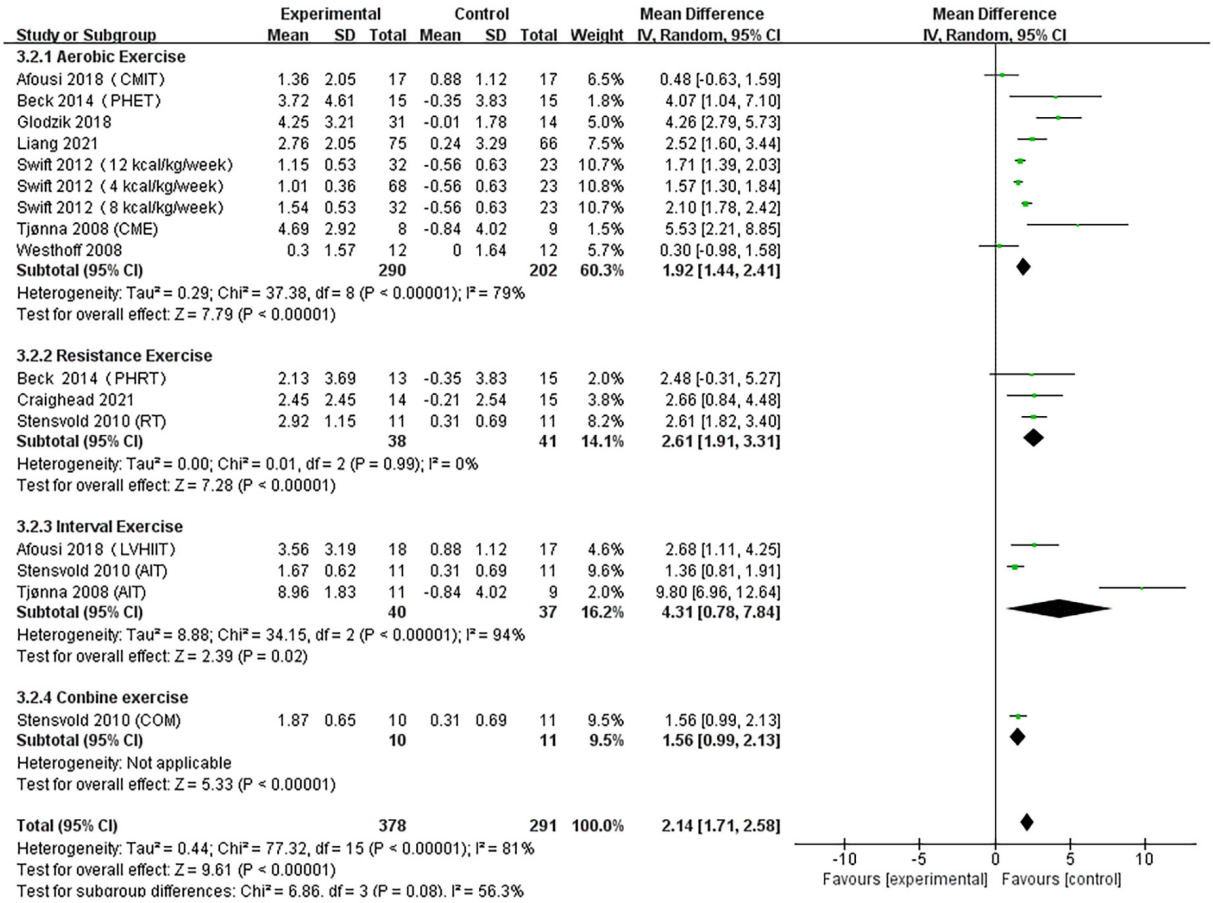

FIGURE 5
Forest plot of postintervention FMD-value comparison between exercise and control groups. SD, standard deviation; Std, standardized; IV, inverse variance; CI, confidence interval.

test $t = -2.33$, $P > 0.031$, and there is publication bias test. We used the trim and fill method to eliminate the publication bias of exercise on SBP. After the trim and fill method was performed, the publication bias was eliminated, the combined effect amount did not change, and there was still a significant difference ($MD = -3.852$, 95% CI, -5.297 to -2.406; $P = 0.000$). The funnel diagram of exercise on FMD was asically symmetrical, Egger's-test P was 0.083, and no publication bias was found. The funnel diagram of exercise on PWV was basically symmetrical, Egger's-test P was 0.770, and no publication bias was found, as shown in **Supplementary Figure 2**.

Discussion

This review summarizes the effects of different exercise modes on vascular function in pre- and hypertensive patients by incorporating relevant RCT studies. The results of this study showed that (1) AE, RT, and HIIT significantly increased FMD and decreased blood pressure in pre- and hypertensive patients; (2) AE, RT, and HIIT were not effective in reducing PWV in pre- and hypertensive patients.

Blood pressure

It is well-known that exercise can reduce blood pressure. Its physiological mechanism is that under the neurohumoral regulation, the activity of sympathetic nerve decreases and the diameter of arterial lumen increases, so as to reduce the resistance of peripheral blood vessels and blood pressure (48). In the current study, AE was the most highly recommended exercise for preventing and improving blood pressure (23). Studies have shown that AE in patients with hypertension can reduce SBP and DBP by about 3.5 and 3 mm Hg, respectively (49). Our study shows that AE significantly reduces blood pressure (SBP –3.51 mm Hg and DBP –2.77 mm Hg) in patients with hypertension, which is similar to the results of previous studies. Early meta-analyses showed that AE reduces

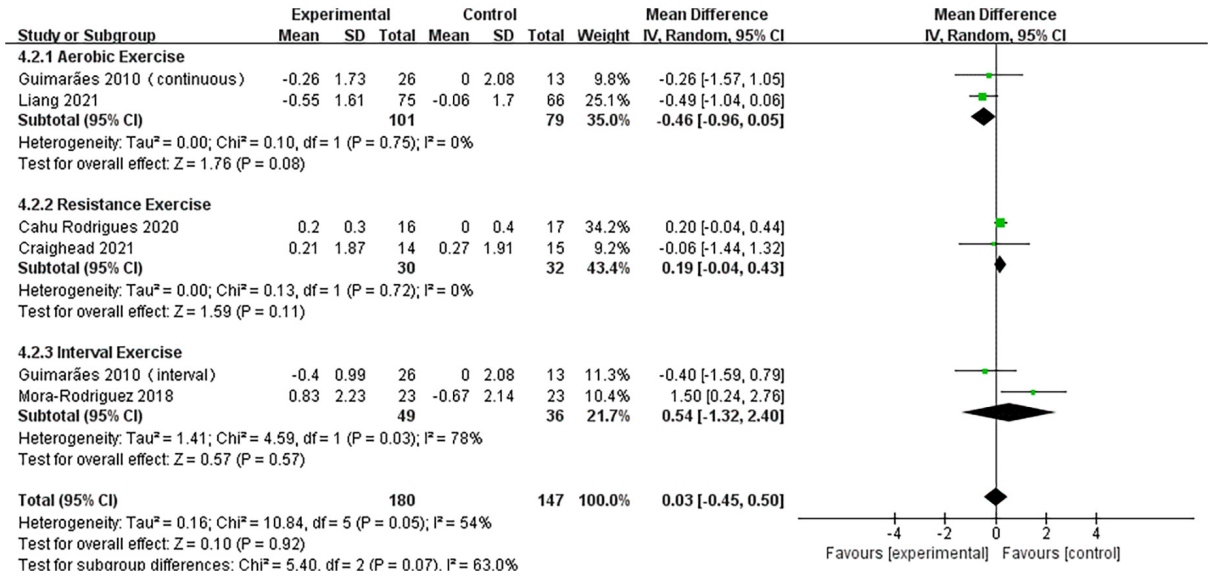

FIGURE 6
Forest plot of postintervention PWV-value comparison between exercise and control groups. SD, standard deviation; Std, standardized; IV, inverse variance; CI, confidence interval.

SBP and DBP in hypertensive patients by reducing vascular resistance and inhibiting the sympathetic nervous system and the renin-angiotensin system (50). The ability of RT to decrease hypertension is debated. Studies have shown that RT can reduce peripheral vascular resistance, thus reducing systemic blood pressure (6, 51). However, some meta-analyses have shown that although RT can reduce blood pressure, it is not as effective as AE (52). Interestingly, our results show that RT is more effective than AE in reducing blood pressure (SBP and DBP were −10.39 and −4.57 mm Hg, respectively) in hypertensive patients, which is quite different from the results of previous studies. However, some studies have shown that RT can reduce blood pressure in hypertensive patients, and the reduction may be similar to that associated with AE (31, 32, 53–56). A recent meta-analysis showed that RT can significantly reduce blood pressure, especially diastolic blood pressure (57). In these four studies, Cahu Rodrigues (10) used isometric handgrip training (IHT) three times a week for 12 weeks, which significantly reduced blood pressure in hypertensive patients (SBP and DBP were −14 and −7 mm Hg, respectively). IHT has attracted increasing attention as a new exercise method for improving hypertension. In recent years, several meta-analyses have shown that IHT treatment can lead to a sustained decrease in blood pressure (58–60). RT's reduction of blood pressure may be due to the increased number of metabolites (vasodilators) in skeletal muscle during and after exercise, such as H^+, ADP, lactate, CO_2, etc., which contribute to the reduction of blood pressure (61). RT can also regulate the changes of systemic blood circulation through autonomic reflex (such as pressure reflex, metabolic reflex, mechanical reflex, chemical reflex, etc.). During resistance exercise, blood pressure increases, vagal-mediated responses are activated, cardiac variability and contractile activity are reduced, peripheral vascular resistance is lowered, inducing systemic vasodilation and thus lowering blood pressure, and this mechanism is continuously activated as resistance exercise progresses, thus helping to keep blood pressure low after exercise (62–64). Previous studies have shown that HIIT can improve the health parameters of patients with cardiovascular disease better than moderate-intensity AE (65, 66). A recent meta-analysis showed that HIIT can promote a greater reduction in blood pressure in healthy adults or hypertensive patients than moderate-intensity continuous exercise (MICE) (67). Our results show that HIIT is more effective than AE in reducing blood pressure in hypertensive patients (SBP and DBP were −4.23 and −4.57 mm Hg, respectively). In contrast to MICE, HIIT results in an increased blood flow to muscle that promotes an increase in endothelial cell shear stress (mechanical stimulation), which promotes the

TABLE 2 Meta-regression analyses on FMD and PWV in studies included in the meta-analysis.

Variables	FMD			PWV		
	N	T	P	N	T	*P*
Medication	9	0.79	0.45	4	0.24	0.82
Baseline SBP ≥ 140 mm Hg	5	2.10	0.06	1	−0.23	0.84
Age ≥ 50	12	0.49	0.63	4	0.77	0.52
Exercise duration ≥ 12 week	3	−0.24	0.81	1	0.58	0.62

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TABLE 3 Subgroup analyses for FMD and PWV in studies included in the meta-analysis.

	FMD				PWV			
Group	***N***	***MD***	I^2	***P* overall change**	***N***	***MD***	I^2	***P* overall change**
Medication	16	2.14	81%	$P < 0.00001$	6	0.03	54%	$P = 0.92$
Yes	9	2.36	85%	$P < 0.00001$	4	0.16	0%	$P = 0.18$
No	7	2.11	73%	$P < 0.00001$	2	−0.17	88%	$P = 0.50$
Baseline SBP	16	2.14	81%	$P < 0.00001$	6	0.03	54%	$P = 0.92$
≥140 mm Hg	5	1.94	55%	$P < 0.00001$	1	−0.49	—	$P = 0.08$
<140 mm Hg	11	2.34	85%	$P<0.00001$	5	0.20	29%	$P = 0.42$
Age	16	2.14	81%	$P<0.00001$	6	0.03	54%	$P = 0.92$
≥50 years	12	2.01	82%	$P < 0.00001$	4	0.27	42%	$P = 0.38$
<50 years	4	2.81	80%	$P<0.00001$	2	−0.46	0%	$P = 0.08$
Exercise duration	16	2.14	81%	$P < 0.00001$	6	0.03	54%	$P = 0.92$
≥12 weeks	3	2.06	80%	$P < 0.00001$	2	0.04	63%	$P = 0.89$
<12 weeks	13	2.76	89%	$P = 0.07$	1	−0.06	—	$P = 0.93$

release of vasodilators such as histamine, and the continuous vasodilator response reduces systemic vascular resistance and blood pressure (68).

Vascular endothelial function

Vascular endothelium is an active and dynamic tissue that can maintain blood circulation, regulate vascular tone, microvascular permeability, signal transduction, angiogenesis, and inflammatory response (69). Vascular endothelial control of vascular tension is regulated by the production and release of mediators such as nitric oxide, prostacyclin, prostaglandin, thromboxane, angiotensin II, endothelin-1, and reactive oxygen species (70). Compared with healthy people, the number of endothelial progenitor cells (EPCs) is reduced in hypertensive patients, which increases the risk of vascular endothelial dysfunction and atherosclerosis in hypertensive patients (71, 72). FMD is an important non-invasive method for measuring vascular endothelial function (73). Regular exercise can improve vascular endothelial homeostasis, mainly by increasing blood flow and shear stress, reducing reactive oxygen species production, and increasing NO availability in endothelial cells (74). Studies have shown that AE can enhance endothelial function by increasing the lateral shear stress of vascular and upregulating endothelial nitric oxide synthase (eNOS) and NO, thus improving FMD (75). Our study shows that AE increases FMD in hypertensive patients. Of the studies included in this paper, Swift's study included only menopausal women performing three different amounts of AE (4 kal/kg/week: *MD* = 1.57, 8 kal/kg/week: *MD* = 2.10, 12 kal/kg/week: *MD* = 1.71) and showed that moderate intensity AE better improved vascular endothelial function in hypertensive patients and that the effect of exercise was similar to the total MD (1.56) (40). In addition, regression and subgroup analyses showed that the positive effect of exercise training on FMD was independent of antihypertensive drug use and that the magnitude of FMD elevation in patients not using drugs was similar to the effect of using drugs. Some studies have suggested that exercise increases FMD because exercise increases blood flow and shear force, enhances the activity of eNOS, and thus increases the formation and bioavailability of NO, thus improving endothelial function (76). Whether RT can improve FMD is still debated. For sedentary people, high-intensity RT can reduce FMD and increase arterial stiffness, whereas moderate-intensity RT can improve endothelial function (33, 34). However, our study demonstrates that RT improves FMD in patients with hypertension. During RT, muscle contractions produces resistance resulting in compression blood vessels and transient ischemia, when muscles relax, the release of blood flow produces congestion and increases flow shear stress (77). Therefore, despite their differences, both AE and RT can improve vascular endothelial function. Studies have shown that HIIT can improve the health indicators of patients with cardiovascular disease better than AE (65, 66). Our study shows that HIIT is more effective than AE in improving FMD in hypertension patients (1.92 for AE and 4.31 for HIIT). The mechanism by which HIIT improves endothelial function in hypertensive patients is not completely clear. Recent studies have shown that HIIT can reduce catecholamine levels and α-adrenergic receptor density and increase NO production and NO bioavailability (36, 78).

Arterial stiffness

PWV refers to the conduction velocity of the pressure wave propagating along the wall of the aorta with each pulse

ejection, and it is a non-invasive index for evaluating the stiffness of arterial vessels. PWV can reflect the elastic state of the aorta system and the middle aorta system (79). Arterial stiffness is determined mainly by three factors: structural elements in the arterial wall, such as elastin and collagen, dilatation pressure, and vascular smooth muscle tension (80). The main physiological features of hypertension include increased hardening of the arteries and decreased vascular compliance. Evidence from animal and human studies suggests that exercise has beneficial effects on vascular compliance and remodeling (81). The mechanism of exercise in improving arterial stiffness is complex. Existing studies have shown that regular exercise increases blood flow and thus imposes higher shear stress on endothelial cells, which in turn leads to increased phosphorylation of eNOS and the production of NO, which has beneficial effects on arteriosclerosis through a series of signal transductions (82). Although many RCTs have demonstrated that all types of exercise can improve vascular endothelial function (83–85), the effects of different exercise patterns on arterial stiffness are debated (86–88). Studies have shown that 12 weeks of AE training at 70–75% HRmax can decrease arterial elasticity in healthy adults (89). Other studies have shown that 12 weeks of AE training at 65–70% HRmax does not improve arterial stiffness s in hypertension patients (90). High-intensity RT can reduce FMD and increase arterial stiffness in sedentary people (34). The results of this study show that exercise is effective in improving FMD in hypertensive patients and does not improve the paradoxical phenomenon of PWV. Few studies have examined why exercise can improve FMD without improving or even aggravating arterial stiffness. The reasons why exercise improves FMD but does not improve or even exacerbate PWV are less well studied, with Soltész et al. (91). reporting a negative correlation between FMD and PWV and Koivistoinen et al. (92) finding no direct correlation between FMD and PWV. Some studies have shown that vascular endothelial function is mediated by rapid changes in cell signals under exercise intervention (93) whereas changes in stiffening of the arteries usually involve remodeling of the extracellular matrix of the arterial wall, which usually takes a long time. For example, AE or other healthy-lifestyle interventions usually take 3 months or more to decrease arterial stiffness (94). Our study concluded that FMD measurements are dependent on changes in vascular endothelial contraction and diastole, and that arterial stiffness is influenced by multiple structural changes in connective tissue proteins within the arterial wall mesothelium, endothelium, and smooth muscle cells (95). Thus, although exercise is effective in improving FMD in hypertensive patients, the impact of improved endothelial function is limited due to hypertension-mediated mechanical stress leading to elastin disruption, collagen deposition, and fibrosis, which leads to progressive arterial stiffness (96), and this chronic sclerosis may take longer to improve or even be irreversible.

Limitations

Although this paper comprehensively explores the effect of different modalities of exercise on the improvement of vascular function in pre- and hypertensive patients. However, there are still shortcomings, and the limitations may have affected this study's conclusions and implications. First, in order to fully reveal the different effects of different exercise modalities on vascular function in pre- and hypertensive patients, this study considered a direct comparison of the effects of different exercise regimens using a net meta, but due to the small amount of included studies, a net meta-analysis could not be performed. Second, the reviewed literature exhibited differences in study design, such as exercise mode and intensity, frequency, and duration of intervention, which may have resulted in this study's heterogeneity. Finally, because few studies have examined combined exercise, no definitive results concerning the effect of combined exercise on vascular function in hypertensive patients could be obtained.

Conclusion and suggestions for future research

The results of this study showed that AE, RT, and HIIT all improved SBP, DBP, and FMD in hypertensive patients, but not PWV, and that this effect was independent of the subjects' medication status, baseline SBP, age and duration of exercise. Although this study found that combined exercise also reduce SBP, DBP, and improved FMD in hypertensive patients, it was not possible to draw strict conclusions about whether combined exercise improved vascular function due to the lack of studies on combined exercise. In order to fully explain the paradoxical phenomenon that exercise enhances FMD without reducing PWV in pre- and hypertensive patients, more research is needed to investigate in depth which exercise modality can improve hypertension-mediated vascular dysfunction and vascular sclerosis, and to provide more scientific and effective exercise programs for hypertensive patients.

Author contributions

HZ and SW: collection, sorting, and analysis of raw materials. HH: thesis design and revision. CZ: critical revision of manuscripts with important knowledge contents. All authors final draft approval.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.1013490/full#supplementary-material

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Association of healthy lifestyle with incident cardiovascular diseases among hypertensive and normotensive Chinese adults

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Background: Whether lifestyle improvement benefits in reducing cardiovascular diseases (CVD) events extend to hypertensive patients and whether these benefits differ between hypertensive and normotensive individuals is unclear. This study aimed to investigate the associations of an overall healthy lifestyle with the subsequent development of CVD among participants with hypertension and normotension.

Methods: Using data from the Suzhou subcohort of the China Kadoorie Biobank study of 51,929 participants, this study defined five healthy lifestyle factors as nonsmoking or quitting for reasons other than illness; nonexcessive alcohol intake; relatively higher physical activity level; a relatively healthy diet; and having a standard waist circumference and body mass index. We estimated the associations of these lifestyle factors with CVD, ischemic heart disease (IHD) and ischemic stroke (IS).

Results: During a follow-up of 10.1years, this study documented 6,151 CVD incidence events, 1,304 IHD incidence events, and 2,243 IS incidence events. Compared to those with 0–1 healthy lifestyle factors, HRs for those with 4–5 healthy factors were 0.71 (95% CI: 0.62, 0.81) for CVD, 0.56 (95% CI: 0.42, 0.75) for IHD, and 0.63 (95% CI: 0.51, 0.79) for IS among hypertensive participants. However, we did not observe this association among normotensive participants. Stratified analyses showed that the association between a healthy lifestyle and IHD risk was stronger among younger participants, and the association with IS risk was stronger among hypertensive individuals with lower household incomes.

Conclusion: Adherence to a healthy lifestyle pattern is associated with a lower risk of cardiovascular diseases among hypertensive patients, but this benefit is not as pronounced among normotensive patients.

KEYWORDS

healthy lifestyle, cardiovascular diseases, ischemic heart disease, stroke, hypertension, prospective cohort study

Introduction

Cardiovascular diseases (CVD) continue to be the leading cause of death and disability globally (1). Moreover, CVD contribute tremendously to the disease burden in China; more than 40% of deaths are attribute to CVD. Ischemic heart disease (IHD) and ischemic stroke (IS) constitute the largest proportions in CVD deaths (2). Meanwhile, as one of the most important independent risk factors for CVD, hypertension had a prevalence rate of 27.5% among Chinese adults in 2018 (3). A third of CVD deaths among hypertensive patients are caused by high blood pressure (4).

It has been demonstrated that avoiding smoking (5), nonexcessive alcohol consumption (6), engaging in adequate physical activity (7, 8), following a healthy diet (9–11), and maintaining a healthy body shape (12) can prevent many cases of CVD in general populations. A healthy lifestyle including these factors was associated with an approximately 43.2% reduction in IHD incidence and a 39.1% reduction in IS incidence among Chinese adults according to previous study (13). However, there is still insufficient research evidence to confirm whether the control of CVD by lifestyle improvement could be extrapolated to hypertensive patients. In addition, it is also unclear whether these healthy lifestyle habits differ between hypertensive and normotensive individuals.

Therefore, this large prospective cohort study aimed to investigate the associations of healthy lifestyle with incidence of CVD, IHD, and IS among Chinese adults with and without hypertension.

Methods

Study population

We used participants' data from the China Kadoorie Biobank (CKB) study in Wuzhong District of Suzhou city, Jiangsu Province. Detailed descriptions of the CKB cohort have been previously published (14–16). We collected informed consent from all participants who completed questionnaires administered by interviewers and had physical measurements taken. The CKB study was approved by the Ethical Review Committee of the Chinese Center for Disease Control and Prevention (Beijing, China), and the Oxford Tropical Research Ethics Committee (University of Oxford, UK).

Overall, a total of 53,269 participants aged 30–79 years were eligible for inclusion. After excluding individuals who had self-reported previous medical histories of cancer ($n = 331$), stroke ($n = 466$), heart disease ($n = 574$) and outliers of duration of hypertension ($n = 8$), current analysis included 51,921 participants.

Assessment of lifestyle factors

In the baseline questionnaire, a variety of lifestyle factors were assessed. Questions about cigarette smoking included smoking status (never, former, or current smoker), amount of daily cigarette smoking for current smokers, and the reason for quitting and years since quitting for former smokers. Alcohol consumption included drinking status (never, former, occasionally, monthly, weekly, or daily); drinkers who drank once or more per week were asked how much alcohol they consumed on a typical drinking day over the past year. The information about physical activity included the common type (occupational-, commuting-, domestic-, and leisure time-related domains) and duration of activities in the past year. Based on the metabolic equivalent tasks (METs) for each activity, we calculated the daily level of physical activity by multiplying the MET value for each activity by hours spent on each activity and summing the MET-hours for all activities (17). Dietary data was collected by a qualitative food frequency questionnaire including 12 conventional food groups in China to assess the habitual dietary intake during the past year. The relative validity and reproducibility of qualitative and quantitative food frequency questionnaires (FFQs) have been validated in previous studies (18). Weight, height, and waist circumference (WC) were measured by trained investigator using calibrated instruments. We calculated body mass index (BMI) as weight (kg)/(height (m)^2).

Assessment of covariates and hypertension

Baseline questionnaire also collected sociodemographic information (age, sex, marital status, highest education level, household income, and occupation), personal and family medical history, time of sedentary behavior, consumption of preserved vegetable and use of antihypertensive drugs. Participants reporting at least one first-degree relative with stroke or heart attack were defined as having a family history of these diseases. Participants were asked how many hours per week they spent watching TV or reading to calculate the time of sedentary behavior per week. Trained staff members used a UA-779 digital monitor to measure blood pressure at least twice, using the mean of the 2 measurements for analyses. Self-reported diabetes or screen-detected diabetes were considered as diabetes mellitus (19). Screen-detected diabetes was defined as measured nonfasting blood glucose ≥11.1 mmol/L or fasting blood glucose ≥7.0 mmol/L (20). Participants with self-reported diagnosis of hypertension by a registered physician, measured systolic blood pressure ≥ 140 mmHg, measured diastolic blood pressure ≥ 90 mmHg, or self-reported use of antihypertensive medication at baseline were classified as having hypertension (4). Duration of hypertension was calculated as age at baseline minus age at diagnosis of hypertension. If hypertension was ascertained by blood pressure at baseline, the duration of hypertension would be considered as 0 year.

Definition of healthy lifestyle

Smoking status, alcohol intake, physical activity, diet, and body shape have been proven to be closely related to the risks of CVD. We included these five lifestyle factors to define a healthy lifestyle (21–24). The healthy group regarding smoking status was defined as nonsmokers or individuals who stopped smoking not resulting from illness (25) because there may be a misleadingly elevated risk while including those who quitted smoking due to illness. For alcohol consumption, the healthy group was defined as never drinkers, weekly drinkers, and moderate daily drinkers (i.e., drinking <25 g of pure alcohol for men and < 15 g for women per day) (26). The healthy group for physical activity was defined as those whose physical activity level was above median after taking age- (<50 years, 50–59 years, and ≥ 60 years) and sex-specific into account. For diet, according to the Chinese Dietary Guidelines and previous findings

(10, 11, 27), six food items were taken into consideration, including vegetables, fruits, eggs, red meat, grains and fish. We created a diet score according to the following criteria: eating vegetables daily, eating fruits daily, eating eggs ≥4 days every week, eating red meat 1–6 days every week, eating grains weekly, eating fish weekly. A score of 1 for those who met the criteria for each food group, a score of 0 otherwise. The diet score ranged from 0 to 6. The healthy group included participants who scored 4 to 6. For body shape, we took body weight and fat into consideration to reflect energy balance. The healthy group was defined as having a moderate BMI ($18.5 \leq BMI \leq 27.9$ kg/m^2) and WC (WC < 90 cm for men and < 85 cm for women). The healthy lifestyle score ranged from 0 to 5. To avoid extreme groups with limited cases, we subsequently categorized the lifestyle scores into four groups (0–1, 2, 3, and 4–5).

Ascertainment of outcomes

Information on CVD incidence cases since baseline recruitment was ascertained from local disease and death registries, the health insurance system, and active follow-up (14). The health insurance system has almost universal coverage and includes detailed descriptions of diagnosis. Street committees conduct annual surveys to supplement the morbidity information of uninsured participants. Trained investigators blinded to baseline information coded all cases with the 10th revision of the International Classification of Diseases (ICD-10). Major cardiovascular events (for stroke, IHD) were reviewed and integrated centrally by cardiovascular specialists from China and the UK.

The primary outcomes were incidences of total cardiovascular diseases (CVD), ischemic heart disease (IHD) and ischemic stroke (IS). Total CVD included all circulatory diseases coded as "I" in ICD-10 (e.g., stroke, any type of heart disease, peripheral vascular disease) and were coded as I00 to I99. IHD and IS were coded as I20 to I25 and I63, which were subdivisions of total CVD.

Statistical analysis

Participants contributed person-years from enrollment into the study until the diagnosis of CVD, loss to follow-up, or December 31, 2017, whichever came first. A Cox proportional hazards model was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of individual and combined lifestyle factors with risks of incidence of total CVD, IHD and IS among participants with or without hypertension. The Cox model was stratified by age at baseline in 5-year intervals.

All lifestyles were included when analyzing individual lifestyle factors. Model 1 was adjusted for sex. Model 2 was additionally adjusted for education level, occupation, marital status, family history of heart attack or stroke, time of sedentary behavior, and usage of antihypertensive drugs. Similarly, we made the same adjustments in the analysis of combined lifestyle factors. We treated the number of healthy lifestyle factors as a continuous variable to analyze the linear trend. Analyses were further stratified by age, sex, education level, household income, occupation, time of sedentary behavior, and usage of antihypertensive drugs for hypertension. The likelihood ratio test including the cross-product term was used to estimate multiplicative interactions. To demonstrate the robustness of our findings, we conducted several sensitivity analyses. First, participants who had diabetes at baseline were excluded. Second, participants whose outcome occurred in the first 2 years of follow-up were excluded. Third, participants whose BMI < 18.5 kg/m^2 were excluded. Forth, for alcohol consumption, the healthy group was redefined as moderate drinking.

R software (version 4.1.0) was used to perform the statistical analyses. A two-sided $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics

Table 1; Supplementary Table S1 show the characteristics of the study participants with or without hypertension (mean age 51.87 years, 58.14% women). Of the 20,194 hypertensive participants, 27.18, 37.84 and 25.31% had 2, 3, and ≥ 4 healthy lifestyle factors, while for the 31,727 normotensive participants, 20.91, 38.77 and 34.62% had 2, 3, and ≥ 4 healthy lifestyle factors. Women were more likely to adhere to a healthy lifestyle. Married participants tended to adhere to fewer healthy lifestyle behaviors.

Associations of individual healthy lifestyle factors with the incidence of cardiovascular diseases

During a median follow-up period of 10.1 years, 6,151 incidence of total CVD cases, 1,304 IHD cases, and 2,243 IS cases were documented. When categorizing the five lifestyle factors into healthy and unhealthy groups (reference group), nonsmoking, being physically active, healthy body weight and fat were each independently associated with a 16, 8, and 10% lower risk of the incidence of total CVD, 18, 20, and 18% lower risk of incident IHD, and 26, 3, and 13% lower risk of incident IS among participants with hypertension, respectively. Those associations were only observed between healthy dietary habits and incident CVD among normotensive participants (Table 2).

Association of a healthy lifestyle pattern with the incidence of cardiovascular diseases

When considering healthy lifestyle factors jointly, compared to those with ≤1 healthy lifestyle scores, the adjusted HRs (95% CIs) of those with 4–5 scores were 0.71 (95% CI: 0.62, 0.81) for the incidence of total CVD, 0.56 (95% CI: 0.42, 0.75) for the incidence of IHD, and 0.63 (95% CI: 0.51, 0.79) for the incidence of IS among hypertensive patients (all p for trend <0.01) (Table 3). When evaluated ordinally, participants having a 1-score increment were related to a greater magnitude of total CVD, IHD and IS risk lowering among hypertensive patients than among normotensive patients. However, there were no significant multiplicative interactions between blood pressure and lifestyle factors on CVD incidence (p for interaction = 0.18 for total CVD, 0.16 for IHD, 0.06 for IS).

TABLE 1 Baseline characteristics of participants according to the number of healthy lifestyle factors.

Baseline characteristics	Number of healthy lifestyle factors				*p* value[b]
	0–1	2	3	4–5	
Hypertension					
No. of participants	1,953 (9.67)	5,488 (27.18)	7,642 (37.84)	5,111 (25.31)	
Age, years	53.40 (9.85)	56.47 (9.78)	56.89 (9.82)	56.36 (9.75)	<0.01
Women	23 (1.18)	2,074 (37.79)	4,853 (63.50)	4,293 (84.00)	<0.01
Married	1,849 (94.67)	5,027 (91.60)	6,819 (89.23)	4,548 (88.98)	<0.01
High school and above	258 (13.21)	466 (8.49)	584 (7.64)	452 (8.84)	<0.01
Household income ≥20,000 RMB/year	1,507 (77.16)	3,718 (67.75)	4,981 (65.18)	3,346 (65.47)	<0.01
Family history of heart attack or stroke	491 (25.14)	1,410 (25.69)	2,067 (27.05)	1,294 (25.32)	0.29
Low-risk lifestyle factors[a]					
Nonsmoking	40 (2.05)	2,374 (43.26)	5,653 (73.97)	4,910 (96.07)	<0.01
Nonexcessive alcohol intake	831 (42.55)	4,492 (81.85)	7,410 (96.96)	5,102 (99.82)	<0.01
Being physically active	232 (11.88)	1,443 (26.29)	3,584 (46.90)	4,379 (85.68)	<0.01
Healthy dietary habits	38 (1.95)	341 (6.21)	1,138 (14.89)	1,906 (37.29)	<0.01
Healthy body weight and fat	561 (28.73)	2,326 (42.38)	5,141 (67.27)	4,715 (92.25)	<0.01
Normotension					
No. of participants	1,807 (5.70)	6,634 (20.91)	12,302 (38.77)	10,984 (34.62)	
Age, years	49.44 (9.33)	50.08 (9.55)	49.25 (9.56)	48.13 (9.47)	<0.01
Women	20 (1.11)	1,701 (25.64)	7,534 (61.24)	9,687 (88.19)	<0.01
Married	1,737 (96.13)	6,307 (95.07)	11,587 (94.19)	10,344 (94.17)	<0.01
High school and above	243 (13.45)	788 (11.88)	1,139 (9.26)	1,117 (10.17)	<0.01
Household income ≥20,000 RMB/year	1,459 (80.74)	5,092 (76.76)	9,487 (77.12)	8,697 (79.18)	<0.01
Family history of heart attack or stroke	336 (18.59)	1,154 (17.40)	2,180 (17.72)	1,939 (17.65)	0.67
Low-risk lifestyle factors[a]					
Nonsmoking	28 (1.55)	1,865 (28.11)	8,286 (67.35)	10,519 (95.77)	<0.01
Nonexcessive alcohol intake	733 (40.56)	5,331 (80.36)	12,028 (97.77)	10,961 (99.79)	<0.01
Being physically active	147 (8.14)	1,727 (26.03)	5,278 (42.90)	9,103 (82.88)	<0.01
Healthy dietary habits	31 (1.72)	340 (5.13)	1,435 (11.66)	4,290 (39.06)	<0.01
Healthy body weight and fat	711 (39.35)	4,005 (60.37)	9,879 (80.30)	10,555 (96.09)	<0.01

Data are presented as means (SDs) for continuous variables or *n* (%) for categorical variables. [a]Healthy lifestyle factors were defined as follows: nonsmoking or having stopped for reasons other than illness; nondaily drinking or daily moderate drinking (drinking <25 g of pure alcohol for men and < 15 g for women per day); engaging in an age- (< 50 years, 50–59 years, and ≥ 60 years) and sex-specific median or higher level of physical activity; diet score ≥4; and having a BMI between 18.5 and 27.9 kg/m^2 and a WC < 90 cm (men)/85 cm (women). [b]Continuous variables were compared by one-way analysis of variance. Categorical variables were compared by Pearson's χ^2 test between different numbers of healthy lifestyles.

Stratified analyses

When stratified by age, sex, education level, household income, occupation, duration of sedentary behavior, and antihypertensive drug use, the analyses yielded consistent results (Figure 1). For participants with hypertension, adults younger than 65 years had a stronger inverse association between healthy lifestyle scores and IHD risk (p for interaction <0.01), and adults with annual household incomes less than 20,000 RMB/year had a stronger inverse association between healthy lifestyle scores and IS risk as well (p for interaction = 0.05).

Sensitivity analyses

Several sensitivity analyses were performed by excluding participants who had diabetes at baseline (Supplementary Table S2), excluding participants whose disease outcomes occurred in the first 2 years of follow-up (Supplementary Table S3), excluding participants whose BMI < 18.5 kg/m^2 (Supplementary Table S4), and only considering moderate drinking as healthy (Supplementary Table S5). The risk estimates did not have materially changes among sensitivity analyses.

Discussion

Principal findings

This large, prospective cohort study of Chinese adults examined the associations of healthy lifestyle scores (i.e., nonsmoking, nonexcessive alcohol intake, being physically active, having a relatively healthy dietary habit, healthy body weight and fat) with the incidence

TABLE 2 Multivariable-adjusted HRs (95% CIs) for incident major cardiovascular diseases (CVD) according to healthy lifestyle factors.

	Hypertension (*n*=20,202)			Normotension (*n*=31,727)		
	Cases/PYs	Model 1	Model 2	Cases/PYs	Model 1	Model 2
Total CVD						
Nonsmoking	2,572/133,556	0.83 (0.75, 0.93)	0.84 (0.75, 0.93)	1,354/225,411	0.87 (0.74, 1.03)	0.87 (0.73, 1.02)
Nonexcessive alcohol intake	3,579/181,386	1.10 (0.99, 1.23)	1.06 (0.95, 1.18)	1,958/313,726	1.11 (0.95, 1.31)	1.10 (0.94, 1.30)
Physically active	1,728/99,070	0.88 (0.82, 0.93)	0.92 (0.85, 0.99)	1,049/175,700	0.91 (0.84, 0.99)	0.97 (0.88, 1.07)
Healthy dietary habits	627/34,930	0.89 (0.82, 0.97)	0.89 (0.81, 0.97)	336/65,796	0.84 (0.74, 0.94)	0.84 (0.74, 0.95)
Healthy body weight and fat	2,512/129,899	0.85 (0.80, 0.91)	0.90 (0.84, 0.96)	1,639/272,008	0.90 (0.81, 1.00)	0.90 (0.82, 1.00)
Ischemic Heart Disease						
Nonsmoking	566/140,577	0.84 (0.67, 1.05)	0.82 (0.66, 1.03)	262/228,943	0.83 (0.58, 1.18)	0.85 (0.59, 1.22)
Nonexcessive alcohol intake	803/190,924	1.33 (1.03, 1.70)	1.25 (0.97, 1.61)	398/318,630	1.85 (1.21, 2.82)	1.85 (1.21, 2.82)
Being physically active	343/104,042	0.75 (0.66, 0.86)	0.80 (0.68, 0.95)	201/178,438	0.88 (0.72, 1.07)	0.92 (0.73, 1.15)
Healthy dietary habits	155/36,540	1.02 (0.85, 1.21)	0.93 (0.77, 1.13)	75/ 66,615	0.97 (0.75, 1.24)	1.03 (0.79, 1.35)
Healthy body weight and fat	534/136,510	0.78 (0.68, 0.89)	0.82 (0.71, 0.94)	315/276,162	0.84 (0.67, 1.05)	0.84 (0.67, 1.05)
Ischemic Stroke						
Nonsmoking	975/139,064	0.73 (0.62, 0.88)	0.74 (0.62, 0.88)	442/228,501	1.03 (0.78, 1.36)	1.05 (0.80, 1.39)
Nonexcessive alcohol intake	1,372/188,928	0.97 (0.81, 1.14)	0.92 (0.78, 1.10)	626/318,008	1.06 (0.81, 1.41)	1.07 (0.81, 1.41)
Being physically active	683/102,747	0.90 (0.81, 1.00)	0.97 (0.86, 1.09)	337/178,105	0.92 (0.79, 1.07)	0.96 (0.80, 1.14)
Healthy dietary habits	232/36,278	0.86 (0.74, 0.98)	0.88 (0.76, 1.02)	103/66,564	0.80 (0.65, 0.99)	0.84 (0.67, 1.04)
Healthy body weight and fat	966/134,935	0.82 (0.74, 0.91)	0.87 (0.79, 0.97)	533/275,553	0.97 (0.81, 1.16)	0.97 (0.81, 1.16)

HRs were calculated in the Cox proportional hazards model. Model 1 was adjusted for sex (men or women); Model 2 was further adjusted for education level (no formal school, primary school, middle school, high school, college, or university or above); marital status (married, widowed, divorced or separated, or never married); household income (<20,000 RMB/Y, 20,000 ~ 34,999 RMB/Y, ≥35,000 RMB/Y); family history of heart attack or stroke (presence, absence, or unknown); consumption of preserved vegetable (never/rarely, monthly, 1–3 days per week, 4–6 days per week, daily); occupation (agriculture/factory/service workers or other); sedentary behavior; and use of antihypertensive drugs (non-use, conversion enzyme inhibitors, β-blockers, diuretics, calcium antagonists and other) and duration of hypertension (for hypertensive population only). All five lifestyle factors were included simultaneously in the same model. Healthy lifestyle factors were defined as follows: nonsmoking or having stopped for reasons other than illness; nondaily drinking or daily moderate drinking (drinking <25 g of pure alcohol for men and < 15 g for women per day); engaging in an age- (<50 years, 50–59 years, and ≥ 60 years) and sex-specific median or higher level of physical activity; diet score ≥4; and having a BMI between 18.5 and 27.9 kg/m^2 and a WC < 90 cm (men)/85 cm (women).

of total CVD, IHD, and IS. Compared with 0 or 1 ideal lifestyle factors, hypertensive patients having a score of 4 or 5 showed a 29, 44, and 37% reduction in the risk of total CVD, IHD, and IS, which was higher than that of normotensive individuals.

Comparison with other studies

Our findings in hypertensive patients are consistent with previous studies in the general population (13, 23, 28–31). In Nurses' Health Study of 15 to 20 years follow-up data, the relative risk (RR) for the healthy lifestyle factors including nonsmoking, daily moderate alcohol consumption, moderate-to-vigorous physical activity, a healthy diet, and BMI under 25 kg/m^2 was 0.25 (95% CI: 0.14, 0.44) for total CVD incidence, 0.17 (95% CI: 0.07, 0.41) for coronary heart disease (CHD) incidence (28), and 0.19 (95% CI: 0.09, 0.40) for IS incidence (29). In Swedish cohorts, a healthy pattern combination of a healthy diet, being physically active, nonsmoking, moderate daily drinking was associated with a population attributable risk of 79% (95% CI: 34, 93%) in myocardial infarction (MI) events among men (23) and a 92% (95% CI: 72, 98%) in MI events among women (30). Lv et al. combined five healthy lifestyles (normal BMI and waist-to-hip ratio, participation in physical exercise, a diet rich in vegetables and fruits and limited in red meat, nonsmoking, and moderate alcohol consumption) to quantify their impacts on IHD and IS incidence in a Chinese population (13). The HR for having 5 to 6 healthy lifestyle factors was 0.50 (95% CI: 0.41, 0.60) for IHD incidence and 0.50 (95% CI: 0.40, 0.64) for IS incidence during the 7.2-year follow-up. However, this protective effect was reduced in the normotensive population in this study. Generally, although many prospective studies have demonstrated the significance of lifestyle interventions for the prevention of CVD, they might have missed patients who already had hypertension. Meanwhile, because adherence to a healthy lifestyle can also reduce the risk of hypertension (32, 33), people without hypertension are recommended to follow a healthy lifestyle as well. Furthermore, due to the potential mediating effect of lipid profile on lifestyle and CVD (34), lipid was not included as a confounder in models, which was consistent with other studies (13, 28–30).

In stratified analyses, the association between healthy lifestyle and IHD risk was stronger among younger participants, and the association with IS risk was stronger among adults with lower household incomes, which was consistent with previous studies (35). These results indicated that people could obtain larger benefits if they adopted healthy lifestyles at an early age or have a lower socioeconomic status. The possible reason may be that individuals of different ages and socioeconomic statuses perceive and choose healthy lifestyles differently, such as people who may choose not to smoke or drink because of financial constraints.

TABLE 3 Multivariable-adjusted HRs (95% CIs) for incident major cardiovascular diseases (CVD) according to lifestyle score category.

Category	Lifestyle score category[b]				*p* for trend	HR (95% CI) per score point	*p* for interaction[c]
	0–1	2	3	4–5			
Hypertension							
Total CVD							0.18
Cases/PYs	385/19,310	1,164/54,960	1,559/77,410	896/53,492			
Model 1	1.00	0.85 (0.76, 0.96)	0.79 (0.70, 0.89)	0.66 (0.58, 0.76)	<0.01	0.89 (0.86, 0.92)	
Model 2[a]	1.00	0.85 (0.76, 0.96)	0.81 (0.72, 0.91)	0.71 (0.62, 0.81)	<0.01	0.91 (0.88, 0.95)	
Ischemic Heart Disease							0.16
Cases/PYs	94/20,265	257/57,890	346/81,647	184/56,022			
Model 1	1.00	0.74 (0.58, 0.94)	0.68 (0.53, 0.87)	0.53 (0.40, 0.70)	<0.01	0.86 (0.80, 0.93)	
Model 2	1.00	0.74 (0.58, 0.95)	0.70 (0.54, 0.90)	0.56 (0.42, 0.75)	<0.01	0.88 (0.81, 0.95)	
Ischemic Stroke							0.06
Cases/PYs	160/20,106	447/57,227	619/80,705	328/55,426			
Model 1	1.00	0.78 (0.64, 0.93)	0.73 (0.61, 0.88)	0.57 (0.47, 0.71)	<0.01	0.86 (0.81, 0.91)	
Model 2	1.00	0.78 (0.65, 0.95)	0.76 (0.63, 0.92)	0.63 (0.51, 0.79)	<0.01	0.88 (0.83, 0.94)	
Normotension							
Total CVD							
Cases/PYs	131/19,002	528/70,474	850/132,814	638/11,9,917			
Model 1	1.00	1.00 (0.82, 1.21)	0.89 (0.74, 1.08)	0.80 (0.65, 0.98)	<0.01	0.91 (0.87, 0.96)	
Model 2	1.00	1.00 (0.82, 1.21)	0.91 (0.75, 1.11)	0.84 (0.68, 1.04)	0.01	0.93 (0.88, 0.98)	
Ischemic Heart Disease							
Cases/PYs	24/19,321	99/71,709	182/134,933	118/121,643			
Model 1	1.00	1.02 (0.65, 1.60)	1.08 (0.69, 1.69)	0.86 (0.54, 1.39)	0.31	0.94 (0.84, 1.06)	
Model 2	1.00	1.05 (0.67, 1.65)	1.16 (0.74, 1.81)	0.97 (0.59, 1.57)	0.73	0.98 (0.87, 1.10)	
Ischemic Stroke							
Cases/PYs	32/19,331	180/71,428	271/134,663	206/121,464			
Model 1	1.00	1.39 (0.95, 2.02)	1.18 (0.81, 1.73)	1.10 (0.74, 1.64)	0.14	0.94 (0.86, 1.02)	
Model 2	1.00	1.39 (0.95, 2.03)	1.22 (0.83, 1.79)	1.17 (0.78, 1.76)	0.39	0.96 (0.87, 1.05)	

[a]HRs were calculated in the Cox proportional hazards model. Model 1 was adjusted for sex (men or women); Model 2 was further adjusted for education level (no formal school, primary school, middle school, high school, college, or university or above); marital status (married, widowed, divorced or separated, or never married); household income (<20,000 RMB/Y, 20,000 ~ 34,999 RMB/Y, ≥35,000 RMB/Y); family history of heart attack and stroke (presence, absence, or unknown); consumption of preserved vegetable (never/rarely, monthly, 1–3 days per week, 4–6 days per week, daily); occupation (agriculture/factory/service workers or other); sedentary behavior; and use of antihypertensive drugs (non-use, conversion enzyme inhibitors, β-blockers, diuretics, calcium antagonists and other) and duration of hypertension (for hypertensive population only). All five lifestyle factors were included simultaneously in the same model. [b]Healthy lifestyle factors were defined as nonsmoking or having stopped for reasons other than illness; nondaily drinking or daily moderate drinking (drinking <25 g of pure alcohol for men and < 15 g for women per day); engaging in an age- (<50 years, 50–59 years, and ≥ 60 years) and sex-specific median or higher level of physical activity; diet score ≥4; and having a BMI between 18.5 and 27.9 kg/m^2 and a WC < 90 cm (men)/85 cm (women). [c]The *p* for interaction was calculated using multiplicative interaction terms and the likelihood ratio test for the interaction between normotension and hypertension.

Previous studies have found that compared to people with moderate alcohol consumption, nondrinkers have an increased risk of CVD (13, 36). Nevertheless, compared to nondrinking, moderate drinking can increase the risk of cancer and injury (37, 38). Therefore, regarding overall human health, our study considered nondrinking as a healthy lifestyle. By classifying both nondrinking and moderate drinking participants into low-risk groups, we found that nonexcessive drinking had no independent protective effect on CVD. Meanwhile, the association between healthy lifestyle and CVD slightly changed after only considering moderate drinking as healthy. The reason may be that genetic variants involved in alcohol metabolism (such as rs671 variant, which is common in east Asian populations and can slow the decomposition of acetaldehyde to causes cardiovascular damage) were different in the two groups (39).

Public health impact

For the primary prevention of CVD, this study's healthy lifestyle pattern provides a positive framework. Our findings contribute valuable information to the prevention of CVD by five modifiable lifestyle factors in hypertensive populations. However, in this study, only less than one-third participants adopted 4 or 5 healthy lifestyles. From a public health perspective, individuals, especially hypertensive patients, could refer to our findings to better understand the significance of CVD prevention and develop healthy lifestyle habits in reference to our findings.

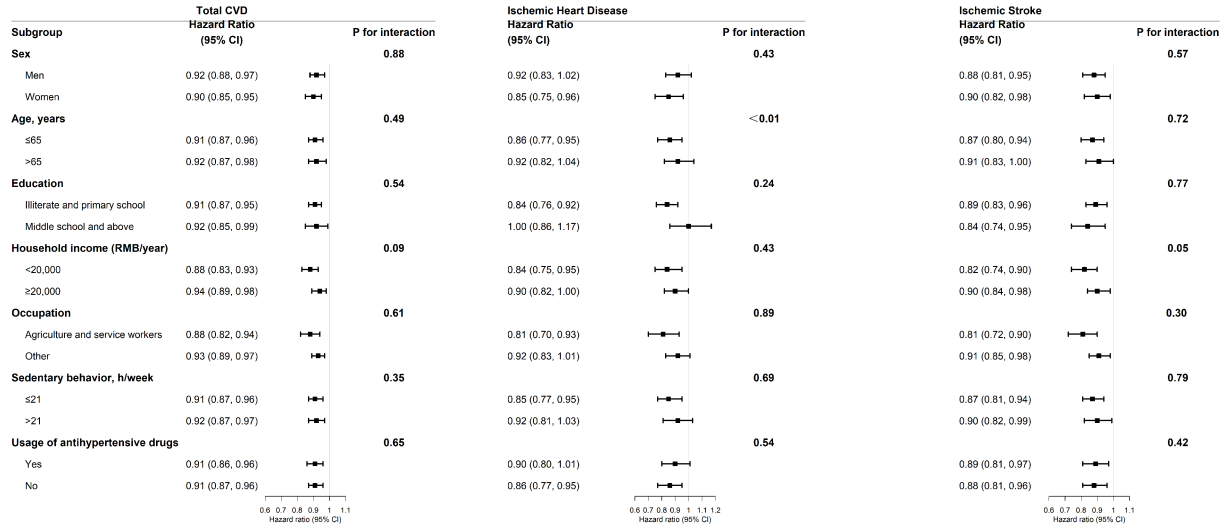

FIGURE 1
Stratified analysis of the association of incident major cardiovascular diseases (CVD) with each 1-unit increment in healthy lifestyle factors in the hypertensive population. This multivariable model was adjusted for sex, education level, marital status, household income, family history of heart attack or stroke, consumption of preserved vegetable, occupation, sedentary behavior, usage of antihypertensive drugs, and duration of hypertension at baseline. The *p* for interaction was calculated using multiplicative interaction terms and the likelihood ratio test.

Strengths and limitations

The strengths of this study included a prospective study design, a relatively large sample size of population, controlling for potential confounding factors, and the use of measured anthropometric information to provide more accurate estimates of blood pressure, BMI and WC (14). Meanwhile, the present study has several limitations. First, lifestyle behaviors were self-reported, which may lead to some misclassification. However, there is no evidence that this type of exposure misclassification is differentially associated with CVD. Second, we created a healthy lifestyle score by using baseline lifestyle information, there is no measurement on the persistence of lifestyles during the follow-up. However, the re-survey conducted during the follow-up showed that there was good agreement between the baseline and re-survey for lifestyle variables (14). Third, confounding such as genetic susceptibility, detailed medication use, or salt and sugar-sweetened beverage intake could not be entirely ruled out. Unmeasured or unknown factors could still cause residual confounding. Forth, some individuals who self-reported taking blood pressure medications at baseline may have met their blood pressure goals at follow-up, which may weaken the difference of protective effects of healthy lifestyles between hypertensive and normotensive population. In addition, information on adherence and persistence to antihypertensive drugs in hypertensive participants could not be confirmed during the follow-up. However, this study calculated the correlation coefficient between healthy lifestyle scores and use of blood pressure medications, and the correlation coefficient is 0.054, indicating that there was little association between taking blood pressure medications and healthy lifestyle scores at baseline (Supplementary Material S5). Finally, this study was observational, and further RCTs are needed to confirm the causal nature of the associations.

Conclusion

This prospective cohort study of Chinese adults provided evidence that adopting a healthy lifestyle pattern, including abstinence from or cessation of smoking, nondaily drinking or daily moderate drinking, adequate physical activity, adherence to a healthy diet, and having a standard BMI and WC, is related to a significantly lower risk of the incidence of total CVD, IHD, and IS among hypertensive participants, but this association is not as pronounced among normotensive individuals.

Data availability statement

The datasets presented in this article are not readily available because the data that support the findings of this study are available from the Department of the China Kadoorie Biobank, but restrictions apply to the availability of these data, which were used under license for the current study and are not publicly available. Data are, however, available from the authors upon reasonable request and with the permission of the Department of the China Kadoorie Biobank. Requests to access the datasets should be directed to https://www.ckbiobank.org/site.

Ethics statement

The studies involving human participants were reviewed and approved by Ethical Review Committee of the Chinese Center for Disease Control and Prevention (Beijing, China) and the Oxford Tropical Research Ethics Committee, University of Oxford (UK). The patients/participants provided their written informed consent to participate in this study.

Author contributions

JS and HG designed the study. HG performed the data analyses and drafted the manuscript. JS revised the data analyses. JS, LC, XF, JZ, MW, and RT critically revised the manuscript for important intellectual content. YL, YH, JJ, YG, JL, PP, and ZC edited and proofread the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1046943/full#supplementary-material

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HEARTS in the Americas clinical pathway. Strengthening the decision support system to improve hypertension and cardiovascular disease risk management in primary care settings

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Background: HEARTS in the Americas is the regional adaptation of the WHO Global HEARTS Initiative. It is implemented in 24 countries and over 2,000 primary healthcare facilities. This paper describes the results of a multicomponent, stepwise, quality improvement intervention designed by the HEARTS in the Americas to support advances in hypertension treatment protocols and evolution towards the Clinical Pathway.

Methods: The quality improvement intervention comprised: 1) the use of the appraisal checklist to evaluate the current hypertension treatment protocols, 2) a peer-to-peer review and consensus process to resolve discrepancies, 3) a proposal of a clinical pathway to be considered by the countries, and 4) a process of review, adopt/adapt, consensus and approval of the clinical pathway by the national HEARTS protocol committee. A year later, 16 participants countries (10 and 6 from each cohort, respectively) were included in a second evaluation using the HEARTS appraisal checklist. We used the median and interquartile scores range and the percentages of the maximum possible total score for each domain as a performance measure to compare the results pre and post-intervention.

Results: Among the eleven protocols from the ten countries in the first cohort, the baseline assessment achieved a median overall score of 22 points (ICR 18 –23.5; 65% yield). After the intervention, the overall score reached a median of 31.5 (ICR 28.5 –31.5; 93% yield). The second cohort of countries developed seven new clinical pathways with a median score of 31.5 (ICR 31.5 –32.5; 93% yield). The intervention was effective in three domains: 1. implementation (clinical follow-up intervals, frequency of drug refills, routine repeat blood pressure measurement when the first reading is off-target, and a straightforward course of action). 2. treatment (grouping all medications in a single daily intake and using a combination of two antihypertensive medications for all patients in the first treatment step upon the initial diagnosis of hypertension) and 3. management of cardiovascular risk (lower BP thresholds and targets based on CVD risk level, and the use of aspirin and statins in high-risk patients).

Conclusion: This study confirms that this intervention was feasible, acceptable, and instrumental in achieving progress in all countries and all three domains of improvement: implementation, blood pressure treatment, and cardiovascular risk management. It also highlights the challenges that prevent a more rapid expansion of HEARTS in the Americas and confirms that the main barriers are in the organization of health services: drug titration by non-physician health workers, the lack of long-acting antihypertensive medications, lack of availability of fixed-doses combination in a single pill and cannot use high-intensity statins in patients with established cardiovascular diseases. Adopting and implementing the HEARTS Clinical Pathway can improve the efficiency and effectiveness of hypertension and cardiovascular disease risk management programs.

KEYWORDS

cardiovascular diseases, hypertension, clinical protocols, critical pathways, public health, quality improvement, implementation science

Introduction

Cardiovascular disease (CVD), mainly ischemic heart disease (IHD) and stroke, causes over 2 million deaths annually in the Americas and has an enormous negative socioeconomic impact (1). Hypertension, the main modifiable risk factor for CVD, affects more than one-third of adults in this region. However, although its treatment is very cost-effective, available, affordable, and safe, only 32.3% of men and 40.9% of women in the Americas have hypertension controlled (blood pressure <140/90 mmHg) (2, 3). Additionally, less than 30% of people with known CVD are treated with evidence-based, proven medications (blood pressure-lowering medications, statins, and aspirin) for secondary prevention (4), underscoring the health system's shortcomings. Indeed, if the Americas improves population-based hypertension control from the current level of 36% to a target of 50%, an estimated 419,924 CVD deaths could be averted (3). Furthermore, if secondary CVD prevention were expanded, many more deaths could be averted.

To address these challenges, the Pan American Health Organization (PAHO) initiated HEARTS in the Americas (5). It is being implemented in 24 countries and over 2,000 primary health care (PHC) facilities. It is a program poised to become the institutionalized model of care for hypertension and CVD risk management in PHC settings by 2025. One of its systematic interventions is implementing a standardized and directive hypertension treatment protocol (6). As a result, most HEARTS countries are moving from hypertension guidelines—without protocols—to standardized treatment protocols based on the best pharmacological options available and affordable in each country. HEARTS protocols emphasize using two antihypertensive medicines from complementary pharmacologic classes in separate pills to initiate treatment upon the diagnosis of hypertension (7). In addition, several countries are taking effective steps to implement a preferred protocol based on a fixed-dose combination (FDC) of antihypertensive drugs in a single pill (8).

At the end of 2021, the WHO released the Guideline for the Pharmacological Treatment of Hypertension in Adults (9). In parallel, HEARTS in the Americas delineated the key drivers for hypertension control (10), a set of specific recommendations to improve the clinical and managerial processes in the PHC setting. Based on these developments, HEARTS in the Americas created a methodology to incorporate these new recommendations resulting in the HEARTS Clinical Pathway for Hypertension and CVD Risk Management, which should help countries update and shape their treatment protocols (11).

This paper aims to describe the main results of a multicomponent, stepwise, and quality improvement intervention designed by the HEARTS in the Americas to support advances in hypertension treatment protocols and evolution towards the Clinical Pathway in countries implementing HEARTS. This intervention is expected to identify improvement areas, reveal the main challenges, and extend best practices through a more standardized and comprehensive approach to hypertension and CVD risk management in PHC. As far as we know, it is the first time that a process of this nature has been carried out and reached so many countries simultaneously. This intervention can serve as an example to other regions of the world to move towards a new clinical and managerial paradigm in hypertension control programs globally.

Materials and methods

Intervention design

HEARTS in the Americas designed a multicomponent, stepwise, and quality improvement intervention. It comprises the following steps: (1) the use of the appraisal checklist to evaluate the current hypertension treatment protocols by external and national experts, (2) a peer-to-peer review and consensus process to resolve discrepancies among external and national experts, (3) a proposal of a clinical pathway to be considered by the countries, and (4) a process of review, adopt/adapt, consensus and approval of the clinical pathway by the national HEARTS protocol committee.

HEARTS in the Americas appraisal checklist and its Clinical Pathway (**Figure 1**) has been published previously (12). Briefly, HEARTS in the Americas established a core advisory group from high and middle-income countries with proven clinical experience in hypertension management (internal medicine, cardiology, nephrology, and public health) and in-depth knowledge of the HEARTS model. The advisory group defined the attributes and components of a preferred treatment protocol, created the appraisal checklist, and delineated the HEARTS

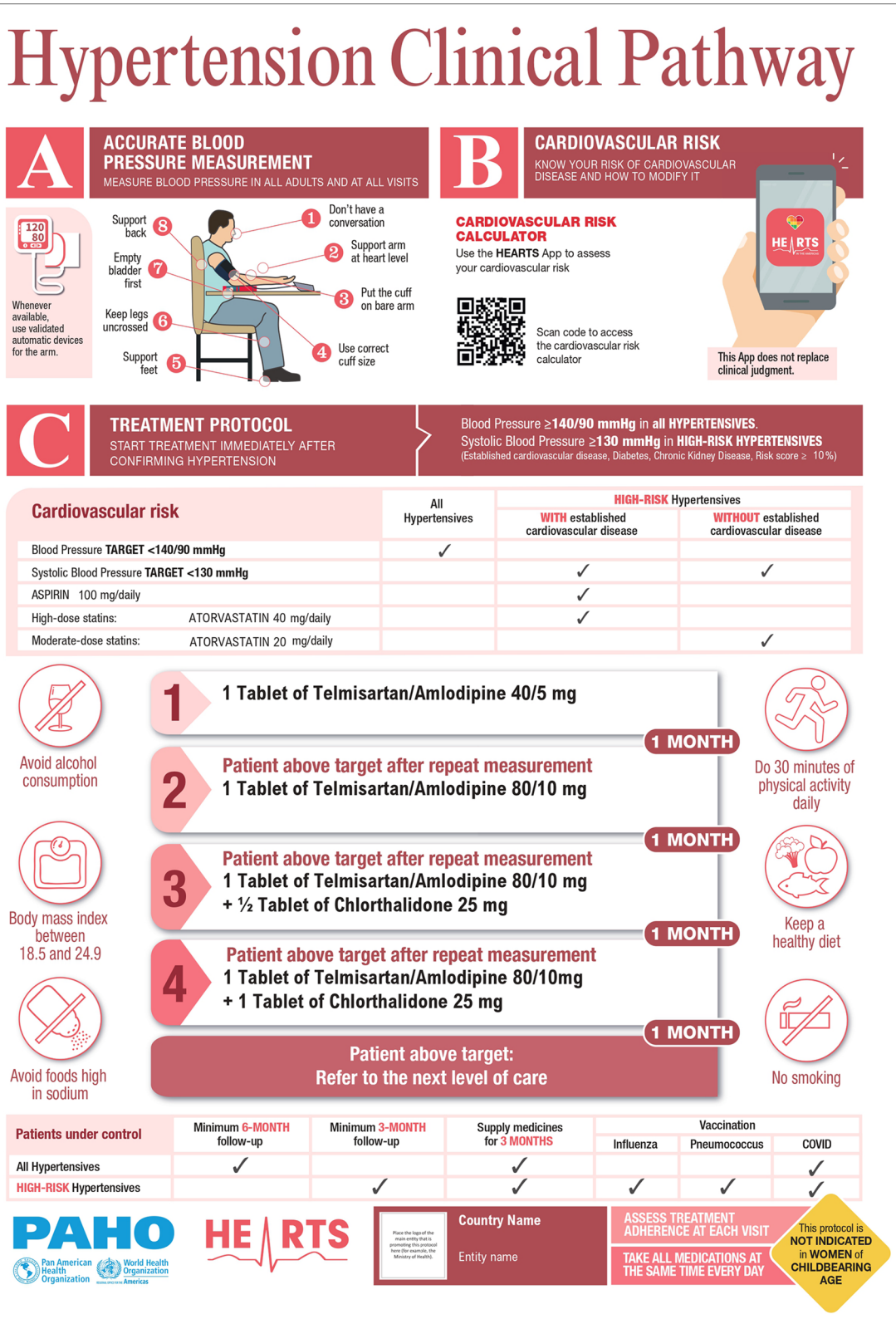

FIGURE 1
HEARTS in the americas hypertension clinical pathway*. *The medications serve as examples and can be replaced with any two medications from any of the three drug classes (ACEis/ARBs, CCBs or thiazide/thiazide-like diuretics). Start with a single-pill combination (fixed-dose combination) or two individual pills if FDC is not available. Figure was prepared by authors. See Ref (11).

Clinical Pathway. The appraisal checklist and the Clinical Pathway were based on the recommendations from the treatment protocol model included in the WHO HEARTS technical package (13), the HEARTS in the Americas specific recommendations to improve treatment protocols (7), the 2021 WHO hypertension guideline (9), and the HEARTS in the Americas key drivers for hypertension control (10).

The HEARTS appraisal checklist is comprised of 34 questions, organized into three domains: (1) requirements to optimize the implementation of a hypertension treatment protocol, (2) blood pressure pharmacologic treatment, and (3) CVD risk management (see **Supplementary Table S1**). All these questions were weighted equally, giving 1 point if the answer was positive, 0 points if negative, and 0.5 points if partial. Therefore, the maximum possible score is 34, composed of the sum of the partial scores of each domain: 15, 10, and 9 possible points, respectively.

Baseline evaluation and intervention

By August 2021, 12 countries that had developed a hypertension treatment protocol were invited to participate in the improvement process. Ten of twelve countries (Argentina, Chile, Cuba, Ecuador, Dominican Republic, Mexico, Peru, Panama, St. Lucia, and Trinidad & Tobago) agreed to participate. In addition, Mexico contributed with two local protocols, one for the State of Chiapas and one for Sonora. As a result, ten countries were included to receive the intervention (first cohort).

First, external experts, using the appraisal checklist, evaluated these 11 protocols. In parallel, experts from each country used the same checklist and did the same process to identify areas for improvement. Then, separate peer-to-peer meetings were held for each country to compare both evaluations, discuss discrepancies, and reach a consensus on the final score. This evaluation resulted in a baseline overall quality score for each protocol. Then, based on the assessment and using the HEARTS Clinical Pathway as a standard, participants' countries committed to initiating a process to adjust their treatment protocols and move toward the clinical pathway standard format.

A second cohort of eight new countries (Bahamas, Bolivia, Brazil, British Virgin Islands, Costa Rica, Dominica, El Salvador, and Guyana), and the state of Yucatan in Mexico, joined HEARTS after evaluation of the protocols had been completed from the first cohort of countries. The second cohort of countries, with no treatment protocols, was trained to use the appraisal checklist to guide the development of their first hypertension protocol under the HEARTS Pathway format.

Post-intervention evaluation

A year later, 16 participants countries (10 and 6 from each cohort, respectively) were included in a second evaluation using the HEARTS appraisal checklist. Fourteen countries defined their clinical pathways, while Argentina and Panama continued to use their previous hypertension treatment protocols. We compared pre and post interventions scores for the first cohort. For the second cohort, it was used in the post-intervention score. The results were aggregated by domain and broken down by country to identify specific areas for improvement and challenges.

Statistical analysis

To compare the results pre and post-intervention, we used two metrics: (a) the median and interquartile scores range, and (b) the percentages of the maximum possible total score for each domain as a performance measure (Flowchart, **Figure 2**). Statistical analyses were performed using a standard software package (Stata, version 13.0; StataCorp).

Results

Overall improvement

Among the eleven protocols from the ten countries of the first cohort, the baseline assessment achieved a median overall score of 22 points (ICR 18–23.5; performance of 65%). After the intervention, the overall score reached a median of 31.5 (ICR 28.5–31.5; performance of 93%). Thus, eight countries moved towards the clinical pathway. Argentina and Panama kept using their previous protocols and made only minor changes to those.

The second cohort of countries assisted by the same expert group, developed seven new clinical pathways (Bolivia, British Virgin Islands, Costa Rica, Dominica, El Salvador, Guyana, and Mexico-Yucatan), with a median score of 31.5 (ICR 31.5–32.5; performance of 93%), comparable to that achieved by the countries from the first cohort. A detailed description of these results is shown in **Figures 3** (by domains) and **4** (by countries) and described below (for additional information, see **Supplementary Tables S2, S3**).

Requirements to optimize the protocol implementation in PHC settings

Under the guiding principle that a clinical pathway must be feasible to implement, the objective was to evaluate and modify its structural aspects to facilitate the program's implementation in a PHC setting. At baseline, protocols of the first cohort reached a median score of 10 (ICR 8.5–10.5; performance of 67%). However, after the intervention, the score increased to a median of 14 (ICR 13.5–14; performance of 93%). This result is due to improvements in the recommendations on clinical follow-up intervals, frequency of medication refills, systematic repetition of blood pressure measurement when the first reading is out of the target, and a more straightforward course of action. In contrast, no country made progress in allowing non-physician health workers, trained and under supervision, to manage antihypertensive treatment while following the approved protocol.

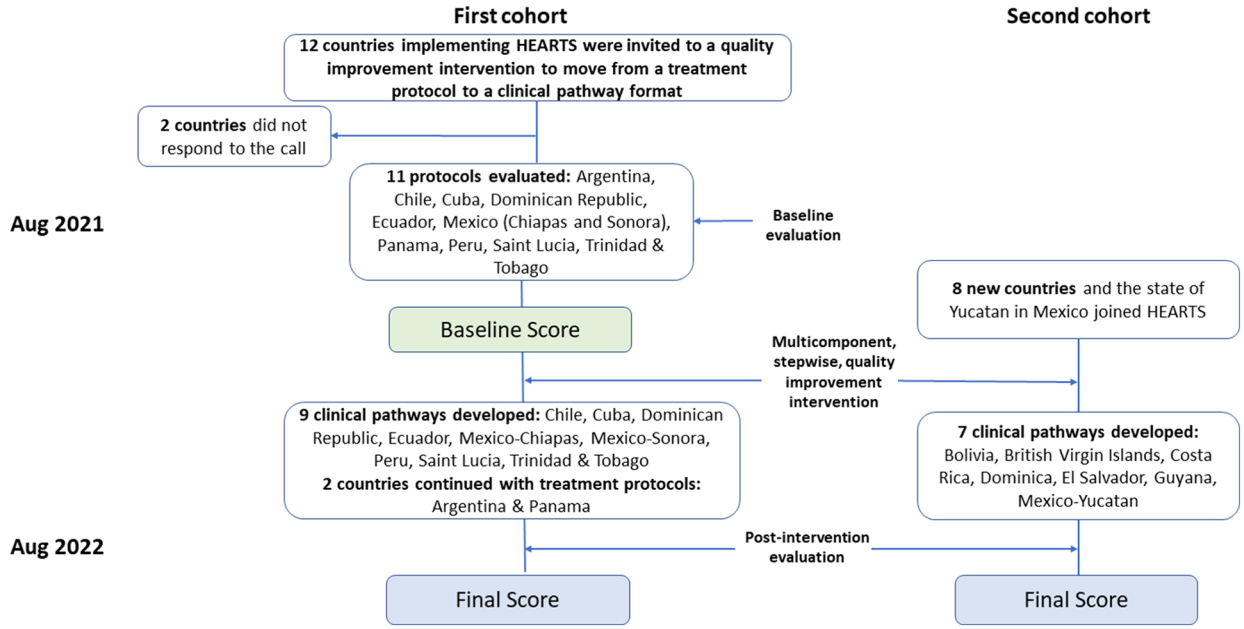

FIGURE 2
HEARTS in the americas. Intervention and evaluation process to move from a standardized hypertension treatment protocol to a CVD risk management clinical pathway.

The second cohort defined their clinical pathways, achieving a median score of 14 (ICR 14–14; performance of 93%). This performance was similar to that of the countries in the first cohort after the intervention. Likewise, its main gap continues to be the lack of regulations allowing antihypertensive treatment management by non-physician health workers.

Blood pressure pharmacologic treatment

This domain includes all items related to hypertension pharmacologic treatment, such as the classes of antihypertensive medication and individual medications within each class, medication doses, and how to use them. At baseline, the first cohort achieved a median score of 7.5 (ICR 6.5–7.5; performance of 75%). However, after the improvement process, the performance increased to a median score of 8.5 (ICR 8–8.5; performance 85%). The main improvements were observed in the recommendation of grouping all medications in a single daily intake and using a combination of two antihypertensive medications for all patients in the first treatment step upon the initial diagnosis of hypertension. However, major gaps persist in the availability of long-acting medications and FDC.

The clinical pathways of the countries included in the second cohort reached a median score for this domain of 8.5 (ICR 8.5–9.5; performance of 85%), similar to that achieved for the countries from the first cohort after the intervention. However, the significant gaps are the same, the lack of availability of long-acting medication and FDC.

In summary, after the intervention, all countries selected medications corresponding to the three first-line pharmacological groups recommended by most, if not all guidelines, including the WHO: angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), dihydropyridine calcium channel blockers (CCBs), and thiazide/thiazide-like agents (TZ-TZL). All countries selected amlodipine as the CCB. Most selected hydrochlorothiazide, except three countries that chose the longer-acting TZL agent, chlorthalidone, and one country chose the TZL agent, indapamide. All countries, except three, started treatment by combining two drugs in separate pills, mainly an ACEI or an ARB, with a CCB or TZ-TZL. Only Saint Lucia, Dominica, and Guyana used an FDC pill (Table 1).

Cardiovascular disease risk management

This domain comprises the CVD risk evaluation, BP thresholds and targets based on CVD risk level, and complementary therapy with aspirin and statins, when appropriate. It showed a greater improvement among the three domains evaluated. Protocols of the first cohort went from a median score of 5 (ICR 2–5.5; performance of 55%) to a median score of 9 (ICR 6.5–9; performance of 100%). The main improvements were in the recommendation of lower BP thresholds and targets in high-risk patients and the recommendation to use aspirin and statins in this population group. However, some countries do not select a

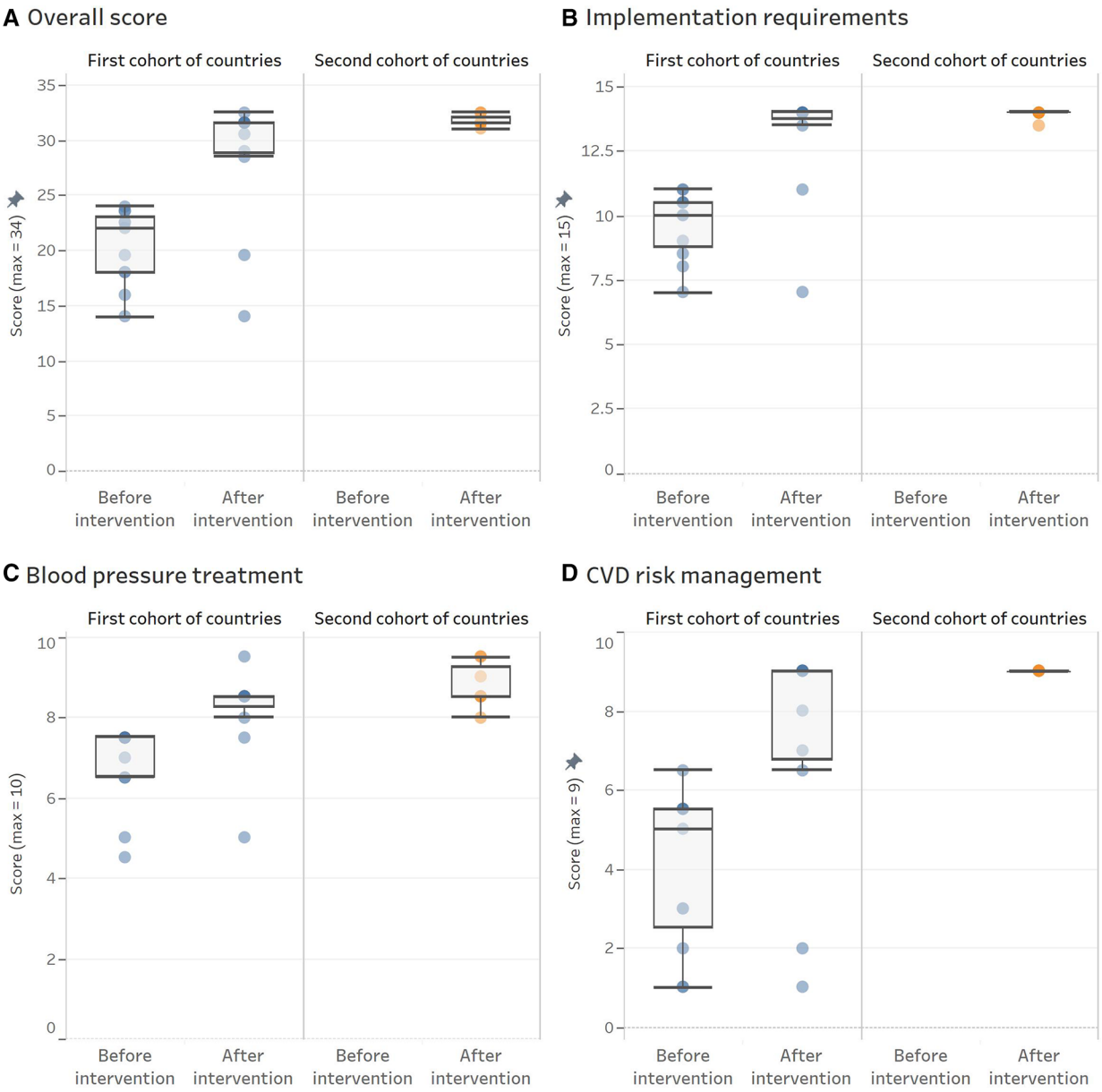

FIGURE 3
HEARTS appraisal checklist overall and domain-specific scores obtained before and after the intervention by cohort of countries. (A) Overall score. (B) Implemenation requirements. (C) Blood pressure treatment. (D) CVD risk management. Each dot represents an evaluated protocol. The overimposed boxplots provide information about the central trend and variation before and after the intervention by cohort of countries. Panel A shows overall scores, and panel B, C, and D presents scores for each domain.

high-intensity statin recommended for treating patients with established CVD. For instance, Argentina and Panama did not include treatment with statins; Peru did not include aspirin and only recommended statins among patients with established CVD. In addition, Dominican Republic and Ecuador, despite including statins in their clinical pathways, did not recommend high-intensity therapy in secondary prevention because both have only simvastatin (**Table 1**). Among the second cohort of countries, the performance of this domain was perfect for all of them, reaching a score of 9.

One of the most innovative additions to the HEARTS Clinical Pathway was the introduction of vaccination against influenza, pneumococcus, and COVID-19. The vast majority of countries incorporated these recommendations.

Discussion

HEARTS in the Americas has advanced across the region due to the leadership of the Ministries of Health, the growing support of professional organizations and civil society, and the generosity of partners and donors (14–16). Likewise, the HEARTS' successful implementation strategy, the innovative and practical solutions to

FIGURE 4
HEARTS appraisal check list scores before and after the evaluation and improvement process by county-protocol.

catalyze health system changes, and the application of a set of guiding principles, all co-created by the participating countries and PAHO, have been relevant (6, 17–19).

Indeed, countries actively participated in the improvement process because HEARTS in the Americas is a community of practice with a shared vision and common goals. Moreover, most countries moved forward in parallel, resulting in clinical pathways with high consistency and minimal clinical variability, because a consensus methodology and standardized checklist were used. Furthermore, the HEARTS Clinical Pathway prototype played a key role in shaping clinical pathways in participating countries. Finally, given that each country developed a process of internal consensus adjusted to local conditions, it is expected that the clinical pathway adopted will progressively become, in addition to a normative document, a widely used and accepted clinical tool feasible to implement in the PHC settings (5, 6, 17).

This study also highlights the challenges that prevent a more rapid expansion of HEARTS in the Americas and confirms that the main barriers are in the organization of health services. For instance, as proof that the system is not fully ready for more innovative changes, and although there is much evidence in its favor (10, 20, 21), drug titration by non-physician health workers, such as nurses and pharmacists, even under the supervision and guidance of an approved treatment protocol, remains a significant issue. Although this topic requires further study, traditions, culture, and normative elements seem to coexist and emerge as barriers that prevent the construction of a more effective and efficient system.

TABLE 1 Medications included in clinical pathways and protocols of the HEARTS countries.

Clinical Pathways and other Treatment Protocols							
HEARTS Countries	Hypertension Treatment Protocol					Concomitant treatment in high-risk patients	
	Step 1	Step 2	Step 3	Step 4	Step 5	Primary prevention	Secondary prevention
Argentina	Amlodipine 5 mg	Amlodipine 5 mg Losartan 50 mg	Amlodipine 5 mg Losartan 100 mg	Amlodipine 10 mg Losartan 100 mg	Amlodipina 10 mg Losartan 100 mg HCTZ 25 mg	No specific recommendation	No specific recommendation
Bolivia	Losartan 50 mg HCTZ 25 mg	Losartan 100 mg HCTZ 50 mg	Losartan 100 mg HCTZ 50 mg Amlodipine 5 mg	Losartan 100 mg HCTZ 50 mg Amlodipine 10 mg		Atorvastatin 20 mg	Atorvastatin 40 mg Aspirin 100 mg
British Virgin Islands	Amlodipine 10 mg	Amlodipine 10 mg Lisinopril 20 mg	Amlodipine 10 mg Lisinopril 40 mg	Amlodipine 10 mg Lisinopril 40 mg Indapamide 1.5 mg		Atorvastatin 20 mg	Atorvastatin 40 mg Aspirin 81 mg
Chile	Losartan 50 mg Amlodipine 5 mg	Losartan 100 mg Amlodipine 10 mg	Losartan 100 mg Amlodipine 10 mg HCTZ 25 mg	Losartan 100 mg Amlodipine 10 mg HCTZ 50 mg		Atorvastatin 20 mg	Atorvastatin 40–80 mg Aspirin 100 mg
Costa Rica[#]	Enalapril 20 mg Amlodipine 5 mg	Enalapril 40 mg Amlodipine 10 mg	Enalapril 40 mg Amlodipine 10 mg HCTZ 25 mg	Enalapril 40 mg Amlodipine 10 mg HCTZ 50 mg		Lovastatin 40–80 mg	Rosuvastatin 20–40 mg Aspirin 100 mg
Cuba[#]	Enalapril 20 mg HCTZ 12.5 mg	Enalapril 40 mg HCTZ 25 mg	Enalapril 40 mg HCTZ 25 mg Amlodipine 5 mg	Enalapril 40 mg HCTZ 25 mg Amlodipine 10 mg		Atorvastatin 20 mg	Atorvastatin 40 mg Aspirin 100 mg
Dominica[*]	Lisinopril 20 mg HCTZ 12.5 mg	Lisinopril 40 mg HCTZ 25 mg	Lisinopril 40 mg HCTZ 25 mg Amlodipine 5 mg	Lisinopril 40 mg HCTZ 25 mg Amlodipine 10 mg		Atorvastatin 20 mg	Atorvastatin 40 mg Aspirin 100 mg
Dominican Republic	Candesartan 16 mg Amlodipine 5 mg	Candesartan 32 mg Amlodipine 10 mg	Candesartan 32 mg Amlodipine 10 mg HCTZ 25 mg	Candesartan 32 mg Amlodipine 10 mg HCTZ 25 mg		Simvastatin 20 mg	Simvastatin 40 mg Aspirin 100 mg
Ecuador	Losartan 100 mg Amlodipine 5 mg	Losartan 100 mg Amlodipine 5 mg Chlorthalidone 25 mg	Losartan 100 mg Amlodipine 5 mg Chlorthalidone 50 mg	Losartan 100 mg Amlodipine 10 mg Chlorthalidone 50 mg		Simvastatin 20 mg	Simvastatin 40 mg Aspirin 100 mg
El Salvador[#]	Enalapril 20 mg Amlodipine 5 mg	Enalapril 40 mg Amlodipine 10 mg	Enalapril 40 mg Amlodipine 10 mg HCTZ 25 mg	Enalapril 40 mg Amlodipine 10 mg HCTZ 50 mg		Atorvastatin 20 mg	Atorvastatin 40 mg Aspirin 100 mg
Guyana[*]	Ramipril 5 mg Amlodipine 5 mg	Ramipril 10 mg Amlodipine 10 mg	Ramipril 10 mg Amlodipine 10 mg HCTZ 25 mg	Ramipril 10 mg Amlodipine 10 mg HCTZ 50 mg		Atorvastatin 20 mg	Atorvastatin 40 mg Aspirin 100 mg
Mexico–Chiapas	Telmisartan 40 mg Amlodipine 5 mg	Telmisartan 80 mg Amlodipine 10 mg	Telmisartan 80 mg Amlodipine 10 mg HCTZ 12.5 mg	Telmisartan 80 mg Amlodipine 10 mg HCTZ 25 mg		Atorvastatin 20 mg	Atorvastatin 40 mg Aspirin 100 mg
Mexico–Sonora	Telmisartan 40 mg Amlodipine 5 mg	Telmisartan 80 mg Amlodipine 10 mg	Telmisartan 80 mg Amlodipine 10 mg HCTZ 12.5 mg	Telmisartan 80 mg Amlodipine 10 mg HCTZ 25 mg		Atorvastatin 20 mg	Atorvastatin 40 mg Aspirin 100 mg
Mexico–Yucatan	Telmisartan 40 mg Amlodipine 5 mg	Telmisartan 80 mg Amlodipine 10 mg	Telmisartan 80 mg Amlodipine 10 mg Chlorthalidone 25 mg			Atorvastatin 20 mg	Atorvastatin 40 mg Aspirin 100 mg
Panama	ACEi or ARB or CCB or TZ at 50% of maximum dose	1 drug at maximum dose or 2 drugs at 50% of maximum dose	2 drugs at maximum dose or 3 drugs at 50% of maximum dose	3 drugs at maximum dose	3 drugs at maximum dose + Spironolactone 12.5 to 25 mg	No specific recommendation	No specific recommendation
Peru[‡]	Losartan 100 mg HCTZ 12.5 mg	Losartan 100 mg HCTZ 12.5 mg Amlodipine 5 mg				No specific recommendation	Atorvastatin 40 mg
Sanit Lucia[*]	Losartan 50 mg Amlodipine 5 mg	Losartan 100 mg Amlodipine 10 mg	Losartan 100 mg Amlodipine 10 mg Chlorthalidone 12.5 mg	Losartan 100 mg Amlodipine 10 mg Chlorthalidone 25 mg		Atorvastatin 20 mg	Atorvastatin 40 mg Aspirin 81 mg

(*continued*)

TABLE 1 Continued

Clinical Pathways and other Treatment Protocols							
HEARTS Countries	Hypertension Treatment Protocol					Concomitant treatment in high-risk patients	
	Step 1	Step 2	Step 3	Step 4	Step 5	Primary prevention	Secondary prevention
Trinidad & Tobago	Lisinopril 10 mg Amlodipine 5 mg	Lisinopril 20 mg Amlodipine 5 mg	Lisinopril 20 mg Amlodipine 10 mg	Lisinopril 40 mg Amlodipine 10 mg Bendrofluazide 2.5 mg		Rosuvastatin 20 mg	Rosuvastatin 40 mg Aspirin 81 mg

ARB, angiotensin receptor blocker; ACEi, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; HCTZ, hydrochlorothiazide; TZ, thiazide/thiazide like agent.
*Uses a single-pill combination of the first two drugs.
#Enalapril is used twice a day.
‡Uses Losartan twice a day and recommends Enalapril as second option.

The HEARTS Clinical Pathway reflects the recommendations of the WHO and the world's best-known hypertension guidelines (9, 22). Indeed, a key qualitative advance in this process has been that most countries have decided to initiate pharmacologic treatment by combining two pills of different, complementary classes in the initial treatment step of the patient with newly diagnosed hypertension. However, a significant barrier to the HEARTS Clinical Pathway is the continued existence of outdated medication formularies. For instance, most countries do not yet include medications that have all of the characteristics of an ideal medication for the treatment of hypertension (8) but instead use the best their national medicine formularies can ensure. Thus, three countries continue to use enalapril, and six continue to use losartan. Indeed, enalapril should be administered twice daily, while losartan, although it can be taken once daily, is the ARB with the shortest half-life (8). Consequently, the lack of long-acting antihypertensive medications and the lack of availability of FDCs in a single pill are significant barriers to achieving a more effective protocol. Indeed, despite the compelling benefits of using FDCs, such as achieving more rapid blood pressure control with significantly greater adherence and persistence to care, neither the countries nor the PAHO's Strategic Fund, an effective pooled procurement mechanism, have yet to obtain competitive prices that allow access to these medicines (23).

Implementing a standardized, straightforward, simple, and directive pharmacologic treatment protocol was a significant step forward in the clinical management of hypertension in the first HEARTS countries. However, a recurring concern from implementing countries is that the treatment protocol seemed too top-down driven and focused primarily on hypertension (11). Certainly, hypertension and diabetes have overlapping risk factors that lead to common pathways of complications and target organ damage. For example, elevated glucose and blood pressure accelerate atherosclerosis, endothelial dysfunction, and vascular injury (24). In addition, these mechanisms give rise to macrovascular (IHD, stroke, aortic disease, and peripheral arterial disease) and microvascular disease (chronic kidney disease, neuropathy, and retinopathy) (25). Therefore, the HEARTS clinical pathway broadens the scope of care and promotes a more integrated approach, including hypertension, diabetes, chronic kidney disease, and secondary CVD prevention in patients with established CVD (26). However, to maximize this opportunity, countries need better access to medications. One key example is the ability to use high-intensity statins in patients with established CVD.

The HEARTS clinical pathway goes further to show its integrative and contemporary essence. For example, despite a well-known association between respiratory infectious diseases and cardiovascular complications (27–29), the vaccination rate among patients at high risk for CVD is very low (30). Therefore, the HEARTS Clinical Pathway incorporated an immunization chart as part of the continuum of care. These recommendations increase the integration between communicable and non-communicable diseases, reinforcing the perspective of vaccination as a preventive strategy for CVD and preparation for future pandemics (31–33). This effort will effectively address the CVD burden, strengthen the resilience of health systems, and defend against the current COVID-19 pandemic and future public health emergencies (34).

Limitations

This approach has important limitations. Notably, the HEARTS clinical pathway does not work in a vacuum or as a stand-alone intervention. On the contrary, it operates as a critical element in a complex health system intervention such as HEARTS. Indeed, any health system intervention to be successful and sustainable requires bold leadership, a skilled and engaged workforce, and a process of learning, acceptance, financially secure, incentives, and continuous quality improvement. Therefore, its sustainability will have to stand the test of time and depends on the health system's maturity and the soundness of the strategies adopted in each context.

Future directions

Adopting and implementing the HEARTS Clinical Pathway in PHC settings can simplify and integrate hypertension management and secondary CVD prevention, improving the efficiency and effectiveness of hypertension programs while optimizing the

pharmaceutical market and supply chain (better and more affordable medicines). In addition, a high-quality, standardized clinical pathway in the context of universal access to healthcare can help address inequalities and disparities in health service delivery by ensuring the best standards for CVD prevention and treatment, regardless of economic and social differences. The institutionalization of the HEARTS clinical pathway should be the next step in the right direction.

Although there is still a long journey ahead between having a good implementation tool -a clinical pathway- and achieving outstanding population control for hypertension, the development and adoption of the clinical pathway by all implementing countries is a milestone in the implementation of HEARTS in the Americas in the path to reduce the burden of the deadliest disease of the contemporary era.

Conclusions

In summary, this study confirms that this quality improvement intervention conducted by HEARTS in the Americas was feasible, acceptable, and instrumental in quickly adopting the new WHO hypertension guideline recommendations and HEARTS key drivers for hypertension control. Almost all countries in the first cohort progressed toward a high-quality clinical pathway. Moreover, the newly implementing countries, including in the second cohort, reached this milestone faster and with less variability. Indeed, progress in all countries and all three domains of the clinical pathway (implementation, blood pressure treatment, and CVD risk management) under evaluation were apparent.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author/s.

Author contributions

AR, DD, JB, and PO: conceived the idea and wrote the original draft. All authors contributed significantly to the design of the methodology, the implementation of the evaluations and assistance to the countries in their improvement processes. RM: contributed significantly to the design and preparation of the figures and tables. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1102482/full#supplementary-material.

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Elevated pulse pressure and cardiovascular risk associated in Spanish population attended in primary care: IBERICAN study

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Introduction: Elevated pulse pressure (ePP) is an independent marker of cardiovascular risk (CVR) in people older than 60, and a functional marker of subclinical target organ damage (sTOD) which can predict cardiovascular events in patients with hypertension (HTN), regardless of sTOD.
Objective: To evaluate the prevalence of ePP in adult population seen in primary care and its association with other vascular risk factors, sTOD and with cardiovascular disease (CVD).
Materials and methods: Observational multicentre study conducted in Spain (8,066 patients, 54.5% women) from the prospective cohort study IBERICAN recruited in Primary Care. Pulse pressure (PP) was defined as the difference between the systolic blood pressure (SBP) and the diastolic blood pressure (DBP) ≥60 mmHg. Adjusted (for age and sex) ePP prevalence were determined. Bivariate and multivariate analyses of the possible variables associated with ePP were carried out.
Results: The mean of PP was 52.35 mmHg, and was significantly higher ($p < 0.001$) in patients with HTN (56.58 vs. 48.45 mmHg) The prevalence of ePP adjusted for age and sex was 23.54% (25.40% men vs. 21.75% women; $p < 0.0001$). The ePP prevalence rates increased linearly with age ($R^2 = 0.979$) and were significantly more frequent in population aged ≥65 than in population aged <65 (45.47% vs. 20.98%; $p < 0.001$). HTN, left ventricular hypertrophy, low estimated glomerular filtration rate, alcohol consumption, abdominal obesity, and CVD were independently associated with ePP. 66.27% of patients with ePP had a high or very high CVR, as compared with 36.57% of patients without ePP (OR: 3.41 [95% CI 3.08–3.77]).
Conclusions: The ePP was present in a quarter of our sample, and it was increased with the age. Also, the ePP was more frequent in men, patients with HTN, other TOD (as left ventricular hypertrophy or low estimated glomerular filtration rate) and CVD; because of this, the ePP was associated a higher cardiovascular risk. In our opinion, the ePP is an importer risk marker and its early identification lets to improve better diagnostic and therapeutic management.

KEYWORDS

hypertension, pulse pressure, cardiovascular risk factors, subclinical target organ damage, hypertensive cardiovascular disease, cardiovascular disease

Introduction

Hypertension (HTN) is an important cardiovascular risk factor (CVRF), both at individual and population levels (1, 2). Its control is important because, after nutritional alterations, HTN ranks second in terms of factors responsible for both worldwide mortality and years of life lost and disability-adjusted life years (3). Its association with other factors multiplies the cardiovascular risk (CVR) (4), which justifies the multifactorial approach to these patients.

The pulse pressure (PP) is an index of the distensibility of the great arteries, and therefore it is a functional marker of subclinical target organ damage (sTOD), it predicts cardiovascular events in patients with HTN (5, 6), and it is an independent marker of CVR in population aged >60 (7).

From a pathophysiological point of view, the early phases of HTN are characterised by changes in the blood circulation of the small blood vessels caused by the systemic vascular resistance. The stiffness of the great vessels increases and they lose elasticity as they age, so a greater pressure is needed which causes left ventricular hypertrophy (LVH). In adults aged <55, the increased vascular resistance results in elevated systolic blood pressure (SBP) and diastolic blood pressure (DBP), and both are predictors of cardiovascular disease (CVD). On the other hand, in people aged >55, the DBP tends to increase until it reaches its peak at the age of 55–60, and then it decreases, in such a way that whereas the DBP decreases, the SBP continues to increase. This would explain the fact that an elevated DBP on its own is less useful as a CVR predictor in older patients, while the prediction of the SBP for CVD is maintained (8).

Kodama et al.'s meta-analysis (9) showed that, in patients with DM, for each 10 mmHg increase, the PP had a higher relative risk of CVD than the SBP, DBP and mean BP. The 33-year follow-up study of the Chicago Heart Association Detection Project (10) showed the predictive usefulness of the PP when it is associated with cerebrovascular disease, coronary heart disease (CHD) and heart failure (HF). The elevation of the PP, caused progressively by ageing, was associated with LVH, albuminuria, carotid intima-media thickness (11) and CVD (12). All this caused that, with age, the elevated pulse pressure (ePP) was more closely correlated with SBP (5, 7, 13).

Like other biological variables, PP is a continuous variable that can increase the absolute risk of cardiovascular events in older subjects (≥50) despite the observed decrease in the relative risk (14). It can also be an independent predictor of mortality from any cause and of coronary origin, especially when the PP reaches values ≥65 mmHg (15), being more remarkable in patients with HTN with high levels of PP (13).

It should be noted that the population with HTN and very high CVR [with diabetes mellitus (DM) and/or previous CVD] has higher values of PP than the rest of patients without DM or CVD (16, 17). Moreover, the hypertensive patients with a PP ≥65 mmHg present LVH or echocardiographic diastolic dysfunction more frequently than those with PP <65 mmHg (18). Finally, a significant proportion of treated hypertensive patients have increased arterial stiffness, a finding that can partly explain the remarkable residual risk of CVD associated even with a well-controlled HTN (19).

It is very important to consider a comprehensive approach to CVR in all patients in primary prevention, before the development of CVD, and which includes the determination of the PP together with the rest of main CVRF. In order to increase knowledge in this regard, the objective of this study is to evaluate, in the context of the IBERICAN study, the presence of ePP in population seen in Primary Care, and its association with other CVRF, sTOD and CVD.

Methods

An observational, cross-sectional analysis was carried out from the inclusion visit of the IBERICAN cohort, which is a multicentre study conducted in Primary Care centres of the Spanish National Health System and whose methodology has been previously published (20). Using consecutive non-probability sampling, 8,066 subjects aged 18–85 were recruited in Primary Care, who consulted their family physician for whatever reason. Blood Pressure was measured with calibrated devices commonly available in clinical practice. The ePP was defined as the difference between SBP and DBP ≥60 mmHg. The rest of variables considered in this study can be found in the additional material.

Statistical analysis

The statistical analysis was performed with the program SPSS® (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.). The qualitative variables were analysed with frequency distribution, percentages, chi squared test, and odds ratios (OR). The continuous variables were evaluated with the determination of the arithmetic means with standard deviation (±SD), median and interquartile range (IQR) of the variables age and PP, *t*-Student test or analysis of variance. The association between variables was estimated with a 95% confidence interval (95% CI) and level of significance $p < 0.05$. The crude prevalences and prevalences adjusted for age and sex were determined through direct method, using standardized 10-year age groups according to the information on the Spanish population aged 18–85 provided by the National Institute of Statistics on July 1st 2021 (21).

To assess the individual effect of comorbidities and CVRF on the dependent variable ePP, a binary unconditional multivariate logistic regression analysis was performed using the backward stepwise method, initially introducing into the model all the variables which showed association in the univariate analysis up to a value of $p < 0.10$, except the variables age, sex and CVR categories which were analyzed individually. The distribution of the specific rates of ePP prevalence by 10-year age groups was analysed using linear regression. Collinearity was previously examined through Spearman's rank correlation coefficient. The model included the

variables that showed correlation coefficients higher than 0.5. Then, the variable that contributed least to the adjustment of the analysis was eliminated in each step. All the tests were considered to be statistically significant if the two-tailed p value was lower than 0.05. A literature search was carried out on PubMed, Medline, Embase, Google Scholar and Web of Science to compare this study with other similar studies published since 1997.

Results

The IBERICAN cohort included 8,066 subjects aged between 18 and 85 (54.5% women), with a mean (±SD) age of 58.41 (±14.83) and a median (IQR) of 59.77 (48.97–69.91) years. The mean (±SD) and the median (IQR) of the PP of the study population were 52.35 (±12.95) mmHg and 50 (43–60) mmHg respectively, where the mean PP was significantly higher ($p < 0.001$) in men [53.65 (±12.50) mmHg] than in women [51.26 (13.21) mmHg]. In patients with HTN, the mean (±SD) and the median (IQR) of the PP were 56.58 (±13.22) mmHg and 55.0 (49.0–64.0) mmHg respectively, where the mean PPs were practically the same ($p = 0.981$) in men [56.58 (±13.17) mmHg] and in women [56.57 (±13.29) mmHg]. In patients without HTN, the mean (±SD) and median (IQR) of the PP were 48.45 (±11.37) mmHg and 50.0 (40.0–55.0) mmHg respectively, where the mean PP in men [50.31 (±10.77) mmHg] was significantly higher ($p < 0.001$) than in women [47.16 (±11.60) mmHg].

The crude prevalence of ePP was 30.03% (95% CI 29.03–31.04), being significantly different ($p < 0.001$) in men [32.55% (95% CI 31.04–34.10)] and in women (27.92% [95% CI 26.60–29.27]). The prevalence of ePP adjusted for age and sex was 23.54% (25.40% in men; 21.75% in women).

The distribution of specific rates of ePP prevalence by 10-year age groups increased with age in a clear way ($R^2 = 0.979$) according to the function $y = 0.095x–0.0194$, being significantly higher in men up to the age group 50–59, and without significant differences in the oldest age groups (Figure 1). The OR of the prevalence of ePP between the populations aged ≥65 and <65 was 2.57 (95% CI 2.23–2.96). The prevalence of ePP in patients aged ≥65 was 45.47% (95% CI 43.67–47.26), which was similar ($p = 0.983$) in men (45.49% [95% CI 42.88–48.09]) and women (45.45% [95% CI 42.99–47.92]). The prevalence of ePP in population aged <65 was 20.98% (95% CI 19.86–22.12), which was significantly different ($p < 0.001$) in men (24.50% [95% CI 22.73–26.28]) and in women (18.16% [95% CI 16.74–19.58]).

The clinical characteristics of the patients with and without ePP are shown in Table 1. All the variables were significantly higher in the population with ePP, except height, total cholesterol and non-HDL cholesterol (with non-significant differences), and the estimated glomerular filtration rate (eGFR) and HDL cholesterol (significantly higher in patients without ePP).

All the CVRF and the comorbidities assessed were significantly associated with ePP, except the variable first-degree family history of early atherosclerotic CVD (ACVD) and smoking (Table 2). The

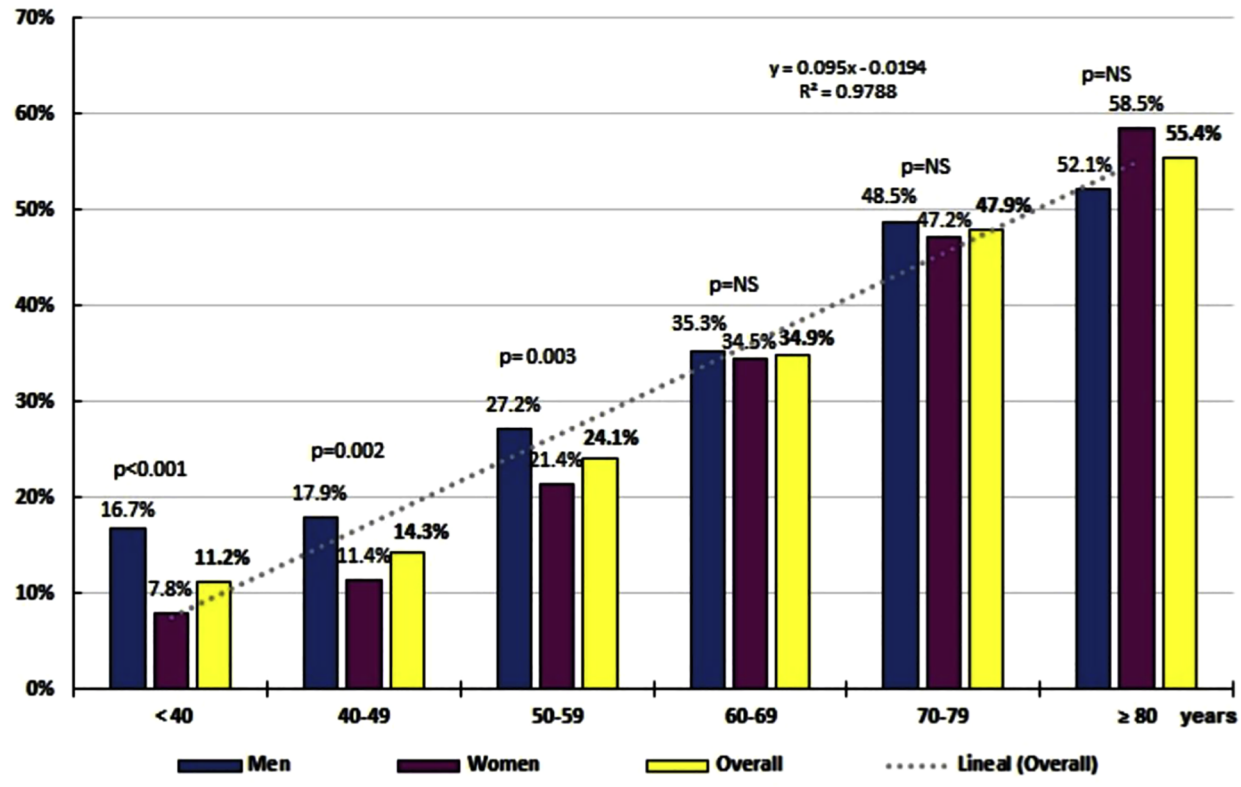

FIGURE 1
Linear correlation between prevalence of elevated pulse pressure (ePP ≥60 mmHg) and age of the IBERICAN cohort.

TABLE 1 Clinical characteristics of populations with and without elevated pulse pressure.

	With PP ≥60 mmHg		With PP <60 mmHg		Difference of means	p^c
	N^a	Mean (±SD)[b]	N^a	Mean (±SD)[b]		
Age (years)	2,422	65.00 (12.82)	5,644	55.58 (14.74)	9.42	<0.001
Weight (kg)	2,422	77.91 (15.24)	5,644	76.16 (15.94)	1.75	<0.001
Height (m)	2,422	1.63 (0.09)	5,644	1.64 (0.09)	−0.01	0.360
BMI (kg/m^2)	2,422	29.25 (5.04)	5,644	28.10 (5.15)	1.15	<0.001
Abdominal girth (cm)	2,394	99.36 (14.86)	5,563	95.21 (14.88)	4.15	<0.001
SBP (mmHg)	2,422	142.93 (13.89)	5,644	123.04 (12.78)	19.89	<0.001
DBP (mmHg)	2,422	75.41 (10.76)	5,644	77.21 (9.81)	−1.80	<0.001
PP (mmHg)	2,422	67.52 (8.92)	5,644	45.84 (8.00)	21.69	<0.001
HR (bpm)	2,422	72.86 (10.94)	5,644	73.50 (10.84)	−0.64	0.013
Fasting blood glucose (mg/dl)[d]	2,422	109.91 (33.36)	5,644	99.04 (25.77)	10.88	<0.001
HbA1c (%)	708	7.14 (1.23)	898	6.95 (1.18)	0.18	0.003
Total cholesterol (mg/dl)[e]	2,422	194.13 (41.35)	5,644	195.60 (55.44)	−1.47	0.127
HDL-C (mg/dl)[e]	2,277	53.73 (15.10)	5,212	55.44 (15.44)	−1.71	<0.001
Non-HDL-C (mg/dl)[e]	2,277	140.74 (40.27)	5,212	141.07 (38.15)	−0.33	0.734
LDL-C (mg/dl)[e]	2,277	116.05 (36.89)	5,212	118.13 (34.81)	−2.08	0.020
Triglycerides (mg/dl)[f]	2,422	131.53 (74.81)	5,644	122.16 (84.19)	9.37	<0.001
Uric acid (mg/dl)	2,099	5.46 (1.48)	4,828	5.16 (1.45)	0.30	<0.001
Creatinine (mg/dl)	2,397	0.90 (0.45)	5,562	0.86 (0.47)	0.04	0.001
eGFR (ml/min/1.73m^2)	2,397	82.05 (19.51)	5,562	90.38 (19.76)	−8.33	<0.001
ACR (mg/g)	1,759	28.39 (95.86)	3,882	18.61 (65.58)	9.78	<0.001

PP, pulse pressure; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR (bpm), heart rate (beats per minute); HbA1c, glycated haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; Non-HDL-C, non-high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate according to CKD-EPI; ACR, albumin-to-creatinine ratio in urine.
[a]*N*: sample size.
[b]SD: standard deviation.
[c]*p*: *p*-value of the difference of means.
[d]To convert from mg/dl to mmol/L, multiply by 0.05556.
[e]To convert from mg/dl to mmol/L, multiply by 0.02586.
[f]To convert from mg/dl to mmol/L, multiply by 0.01129.

ePP was significantly ($p < 0.001$) more frequent in patients with HTN (41.65% [95% CI 40.09–43.20]) than in patients without HTN (19.28% [95% CI 18.09–20.48]) (OR: 2.99 [2.70–3.30]), and mainly in patients with SBP/DBP ≥140/90 mmHg (64.66% [95% CI 62.34–66.98]) as compared with those who had SBP/DBP <140/90 mmHg (24.99% [95% CI 23.20–26.78]) (OR: 5.49 [4.78–6.31]). Among the population with HTN, the proportion of patients who had ePP was similar ($p = 0.678$) in men (41.32% [95% CI 39.12–43.52]) and in women (41.98% [95% CI 39.75–44.20]). The other CVRF and comorbidities which showed greater degree of association were LVH, HF, low eGFR (<60 ml/min/1.73m^2) and DM (**Figure 2**). In the multivariate analysis, the CVRF and comorbidities which were independently associated with ePP were HTN, LVH, DM, low eGFR, alcohol consumption, abdominal obesity and cardiovascular diseases (**Table 3**).

66.27% (95% CI 64.38–68.15) of patients with ePP had a high or very high CVR, as against the patients without ePP, of whom 36.57% (95% CI 35.31–37.83) had a high or very high CVR (OR: 3.41 [95% CI 3.08–3.77]) (**Table 2**, **Figure 2**).

Discussion

This subanalysis of the cohort of the IBERICAN study describes the characteristics of the population according to the presence of ePP, with a prevalence adjusted for age and sex of 23.5%. This prevalence increases with age, is higher in men, and is more frequently associated with HTN, DM, low eGFR, LVH and HF, which increases the CVR of patients with ePP.

After a detailed revision of bibliography, our results represents the first time that are described the prevalence of ePP and its associations with other cardiovascular risk factors, TOD and CVD simultaneously in the same cohort, using a clínica population, recruited in primary care.

The prevalence of ePP observed in our study (23.5%) are similar to observed in other studies as NHANES survey (26.91%) using PP > 55 mmHg in a sample with 5,771 subjects (22) or 12.1% of patients aged <55 and 27.8% of those aged ≥55 in a French study about a sample with 19,083 men (15). The main variable associated with ePP prevalence was the age, with a quasi-perfect linear correlation, variable also associated with the cardiovascular mortality (25), and in older 60 years the ePP has an important predictive value of the cardiovascular risk (26).

The relationship between ePP and other variables as HTN o LVH was described by Vasan et al. that described the association of these TOD with central PP (12). In the same line, other studies analysed the role of ePP in the develop of chronic kidney disease (CKD) (23) or other organ targeting as HF (24). These associations of the ePP can explain that we observed

TABLE 2 Factors and comorbidities in populations with and without elevated pulse pressure.

	PP ≥60 mmHg		PP <60 mmHg		p^C
	N^a	%(95% CI)[b]	N^a	%(95% CI)[b]	
Current smoking	364	15.03 (13.61–16.45)	1047	18.55 (17.54–19.56)	<0.001
Sedentary lifestyle	791	32.66 (30.79–34.53)	1580	27.99 (26.82–29.11)	<0.001
Alcohol consumption	365	15.11 (13.69–16.54)	669	11.93 (11.08–12.78)	<0.001
Overweight	1288	53.29 (51.28–55.29)	2563	45.50 (44.20–46.80)	<0.001
Obesity	975	40.26 (38.29–42.22)	1746	30.94 (29.73–32.15)	<0.001
Abdominal obesity	1501	62.70 (60.76–64.64)	2926	52.60 (51.29–53.91)	<0.001
Diabetes	718	29.64 (27–83–31–46)	906	16.05 (15.09–17.01)	<0.001
Hypertension	1608	66.56 (64.67–68.44)	2253	39.98 (38.70–41.26)	<0.001
Dyslipidemia	1401	58.04 (56.07–60.01)	2650	47.04 (45.74–48.35)	<0.001
TG/HDL-c > 2	1298	57.00 (54.94–59.02)	2570	49.31 (47.94–50.66)	<0.001
Premature CVD FH	375	16.86 (15.31–18.42)	792	15.27 (14.30–16.25)	0.086
LVH	162	6.69 (5.69–7.68)	155	2.75 (2.32–3.17)	<0.001
ABI ≤0,9	60	2.48 (1.86–3.10)	89	1.58 (1.25–1.90)	0.006
Low eGFR	316	13.18 (11.83–14.54)	358	6.44 (5.79–7.08)	<0.001
Albuminuria	252	10.40 (9.19–11.62)	363	6.43 (5.79–7.07)	<0.001
CKD	406	23.08 (21.11–25.05)	555	14.30 (13.20–15.40)	<0.001
sTOD	626	26.12 (24.36–27.87)	831	14.94 (14.00–15.88)	<0.001
Coronary heart disease	233	9.62 (8.45–10.79)	350	6.20 (5.57–6.83)	<0.001
Stroke	134	5.53 (4.62–6.44)	189	3.35 (2.88–3.82)	<0.001
PAD	121	5.00 (4.13–5.86)	144	2.55 (2.14–2.96)	<0.001
Heart failure	120	4.95 (4.09–5.82)	129	2.29 (1.90–2.68)	<0.001
Atrial fibrillation	137	5.66 (4.74–6.58)	201	3.56 (3.08–4.04)	<0.001
ACVD	429	17.71 (16.19–19.23)	619	10.97 (10.15–11.78)	<0.001
CVD	599	24.73 (23.01–26.45)	868	15.38 (14.44–16.32)	<0.001
Low CVR	268	11.11 (9.85–12.36)	2125	37.81 (36.54–39.08)	<0.001
Moderate CVR	546	22.63 (20.96–24.30)	1440	25.62 (24.48–26.76)	0.004
High CVR	475	19.69 (18.10–21.27)	979	17.42 (16.43–18.41)	0.015
Very high CVR	1124	46.58 (44.59–48.57)	1076	19.15 (18.12–20.17)	<0.001

[a]N: sample size.
[b]95% CI: 95% confidence interval.
[c]p: p-value.
PP, pulse pressure; TG/c-HDL, triglycerides/HDL-cholesterol; CVD FH, first-degree family history of premature cardiovascular disease (<55 years [men]; <65 years [women]); LVH, left ventricular hypertrophy; ABI, ankle-brachial index; albuminuria, albumin-creatinine ratio (ACR)≥30 mg/g (including proteinuria, ACR >300 mg/g); low eGFR, glomerular filtration rate <60 mL/min/1.73m^2 estimated according to CKD-EPI; CKD, chronic kidney disease (low eGFR and/or albuminuria); sTOD, subclinical target organ damage (LVH, albuminuria, low eGFR, ABI ≤0.9); PAD, peripheral artery disease, ABI ≤0.9; ACVD, atherosclerotic cardiovascular disease (coronary heart disease, stroke, PAD); CVD (cardiovascular disease), ACVD, heart failure, atrial fibrillation; CVR, cardiovascular risk according to SCORE. *(Consult additional material for reference-checking).*

two-thirds of the patients with ePP had higher cardiovascular risk, in the same line observed in the MRFIT study that described the association between PP and cardiovascular mortality in hypertensive patients (27).

These relationships with other cardiovascular risk factor, TOD and CVD describes the ePP as a early risk marker and the importance of and early identification to introduce changes in the treatment of the patients and improve their prognosis. In really, maybe we need more studies, and clinical trials, that confirm that this reduction of PP would reduce the cardiovascular events and mortality.

Strengths and limitations

This subanalysis of the IBERICAN study has certain limitations derived from its very design and from the interpretation of some of the variables. The study sample has the bias of being a clinical cohort between the age of 18 and 85 seen in Primary Care with a possible accumulation of risk factors and comorbidities as compared with the rest of the population. Thus, the results obtained could be only extrapolated to the clinical population, despite the validity of the associations found. This study does not differentiate whether the ePP was detected during the day or at night, even though the ePP is associated with LVH regardless of the moment of detection whereas the greatest increase of ventricular mass has been associated with ePP during night time. Like SBP and DBP, PP is a continuous variable, so the decision to establish the ePP at an easy-to-remember threshold of 60 mmHg is an arbitrary one, though justified by the available literature (28, 29). The analysis of the variable ACVD (CHD, stroke and PAD) does not differentiate between type-1 (atherothrombotic) and type-2 (non-atherothrombotic) coronary ischemic heart disease, or between ischemic strokes and hemorrhagic strokes. From a strictly clinical point of view, our results can be considered to show the relationship between the set of processes included in the variable ACVD and ePP,

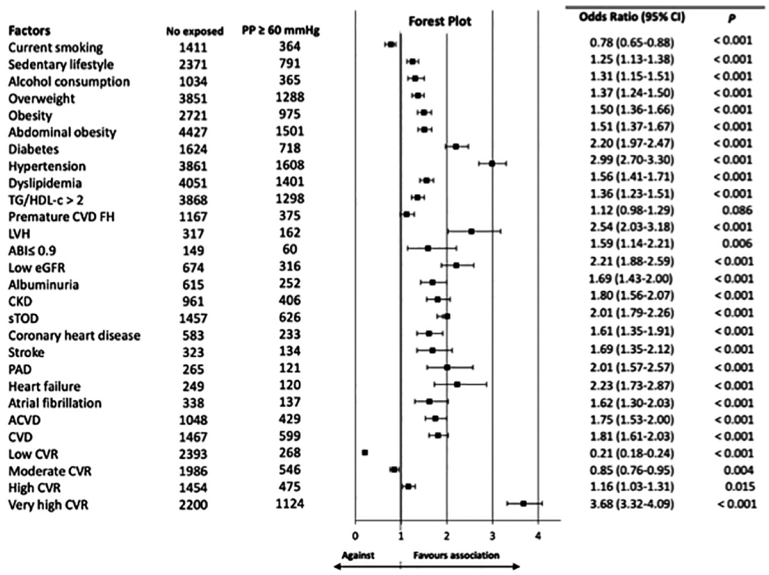

FIGURE 2
Forest Plot representation of associations between various factors and ePP in the IBERICAN cohort ePP, elevated pulse pressure; PP pulse pressure; TG/c-HDL, triglycerides/HDL-cholesterol; CVD FH, first-degree family history of premature cardiovascular disease [<55 years (men); <65 years(women)]; LVH, left ventricular hypertrophy; ABI, ankle-brachial index; albuminuria, low eGFR: glomerular filtration rate <60 ml/min/1.73 m^2 estimated according to CKD-EPI; albumin-creatinine ratio (ACR) 30 mg/g (including proteinuria: ACR > 300 mg/g); CKD, chronic kidney disease (low eGFR and/or albuminuria); sTOD, subclinical target organ damage (LVH, albuminuria, low e GER, ABI a0.9); PAD, peripheral artery disease, ABI ≤0.9; ACVD, atherosclerotic cardiovascular disease (coronary heart disease, stroke, heart failure, atrial fibrillation, PAD); CVD cardiovascular disease; CVR, cardiovascular risk according to SCORE. 95% CI: 95% confidence interval; p, p-value.

because the existence of such association has been previously demonstrated not only with atherothrombotic disease but also with hemorrhagic strokes (30) and with non-obstructive coronary ischemia in stressful situations (31).

Among the strengths of this study are the large sample of the IBERICAN cohort, the adjustment for age and sex of the prevalence rates (which makes it easier to compare the results with other populations), the assessment of the association of ePP with numerous cardiovascular, cardiometabolic and renal variables, and the presentation of relevant results on ePP which did not exist in Spain before.

Clinical implications

There are no well-designed intervention studies which assess the potential cardiovascular benefits of specific therapeutic strategies for ePP. This may justify the fact that no PP objectives or appropriate treatment has been established. It has been found that the levels of PP reached with antihypertensive treatment form a curved (J-shaped) association for most cardiovascular events, and a linear one when it was associated with myocardial infarction, setting the optimum level of PP at 50 mmHg (32). A strict control of BP lowers the PP levels in varying degrees

TABLE 3 Multivariate analysis of risk factors and comorbidities associated with elevated pulse pressure (≥60 mmHg).

ACVD model	β^a	OR Exp (β)^b	p^c	CVD model	β^a	OR Exp (β)^b	p^c
Hypertension	0.88 (0.06)	2.41 (2.16–2.68)	<0.001	Hypertension	0.87 (0.06)	2.93 (2.14–2.67)	<0.001
LVH	0.48 (0.12)	1.62 (1.27–2.05)	<0.001	LVH	0.46 (0.12)	1.58 (1.25–2.01)	<0.001
Diabetes	0.43 (0.06)	1.53 (1.36–1.73)	<0.001	Diabetes	0.42 (0.06)	1.53 (1.35–1.72)	<0.001
Low eGFR	0.39 (0.09)	1.48 (1.25–1.75)	<0.001	Low eGFR	0.38 (0.09)	1.46 (1.23–1.73)	<0.001
Alcohol consumption	0.22 (0.07)	1.25 (1.08–1.45)	0.002	Alcohol consumption	0.22 (0.07)	1.25 (1.08–1.45)	0.002
ACVD	0.20 (0.07)	1.23 (1.06–1.41)	0.006	CVD	0.20 (0.06)	1.22 (1.07–1.38)	0.002
Central obesity	0.12 (0.05)	1.13 (1.02–1.26)	0.023	Central obesity	0.12 (0.05)	1.13 (1.01–1.25)	0.029

LVH, left ventricular hypertrophy; low eGFR, glomerular filtration rate <60 ml/min/1.73m^2 estimated according to CKD-EPI; ACVD, atherosclerotic cardiovascular disease (coronary heart disease, stroke, peripheral artery disease); CVD (cardiovascular disease), ACVD, heart failure, atrial fibrillation.
[a]β coefficient (± deviation).
[b]Odds-ratio Exp (β) (95% confidence interval).
[c]p: p-value of Wald test with one degree of freedom.

according to the drug treatment used (**Supplementary Figure S3** in the additional material). Emphasis should be placed on individualising HTN treatments, especially in patients with CHD (even in its silent forms), DM or fragile elderly patients, since an excessive reduction of both the SBP and DBP may lead to new cardiovascular events (33–38).

Conclusions

The observational multicentre IBERICAN study, recruited in primary care in Spain, showed that near a quarter of the patients had ePP, and this prevalence increases with the age of the patients.

The prevalence of ePP showed an independent association with other cardiovascular risk factors, as HTN, diabetes, abdominal obesity and alcohol consumption; other TOD, as LVH and low eGFR; and CVD.

This association with other cardiovascular determinants and the higher cardiovascular risk associated become the ePP in the interesting risk marker to identify in the clinical practice to introduce more intensive treatments to improve the cardiovascular prognosis. However, this affirmation needs to be confirmed in a prospective observational studies and clinical trials.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

Ethics statement

This study was conducted according to the guidelines of the Declaration of Helsinki and approved by the ECCR of Hospital Clínico San Carlos in Madrid on February 21, 2013 (C.P. IBERICAN-C.I. 13/047-E) and is registered in https://clinicaltrials.gov with the number NCT02261441. The information obtained was treated with absolute confidentiality, respecting the principles of the Declaration of Helsinki. Participants' EHR data was anonymized upon extraction. All patients, when invited to be included in the health system through their personalized identification system (PIS), give their authorization to the Regional Ministry of Health (RMoH) so that the information contained in their EHR can also be used for research purposes, in compliance with data protection regulations.

Author contributions

Conceptualization, methodology, writing—review and editing: AM-A, AR-G, VP-C, AS-C, MP-D, AS-F and SC-S; writing—original draft preparation: AM-A, AR-G, VP-C, and AS-C; supervision: AM-A, AR-G, VP-C, AS-C, MP-D, AS-F and SC-S; project administration: SC-S; funding acquisition: AM-A, AR-G, VP-C, AS-C, MP-D, AS-F and SC-S. All authors contributed to the article and approved the submitted version.

Group members of the IBERICAN study

The full list of members can be found in the **Supplementary material**.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1090458/full#supplementary-material.

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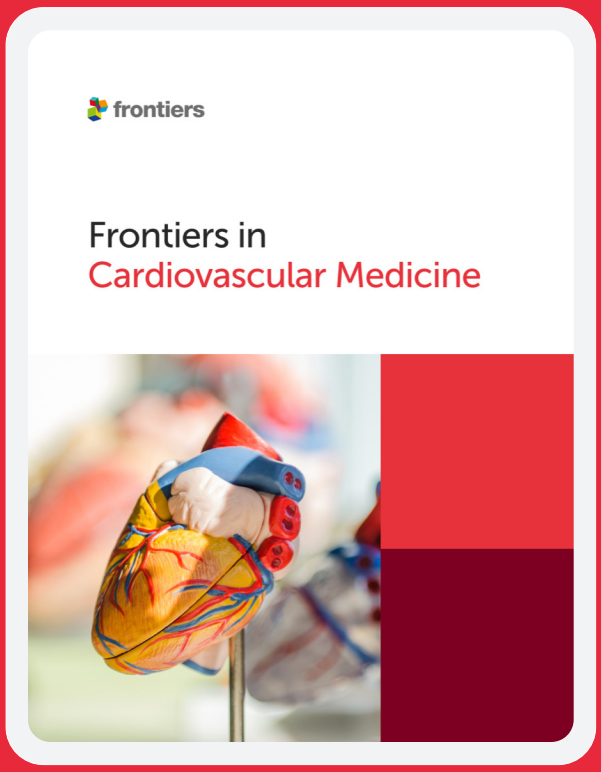

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