Circulation

ORIGINAL RESEARCH ARTICLE

Sex Differences in Primary and Secondary Prevention of Cardiovascular Disease in China

BACKGROUND: Despite improvements in diagnostic and therapeutic interventions to combat cardiovascular disease (CVD) in recent decades, there are significant ongoing access gaps and sex disparities in prevention that have not been adequately quantified in China.

METHODS: A representative, cross-sectional, community-based survey of adults (aged ≥45 years) was conducted in 7 geographic regions of China between 2014 and 2016. Logistic regression models were used to determine sex differences in primary and secondary CVD prevention, and any interaction by age, education level, and area of residence. Data are presented as adjusted odds ratios (ORs) and 95% CIs.

RESULTS: Of 47 841 participants (61.3% women), 5454 (57.2% women) had established CVD and 9532 (70.5% women) had a high estimated 10-year CVD risk (≥10%). Only 48.5% and 48.6% of women and 39.3% and 59.8% of men were on any kind of blood pressure (BP)–lowering medication, lipid-lowering medication, or antiplatelet therapy for primary and secondary prevention, respectively. Women with established CVD were significantly less likely than men to receive BP-lowering medications (OR, 0.79 [95% CI, 0.65–0.95]), lipid-lowering medications (OR, 0.69 [95% CI, 0.56–0.84]), antiplatelets (OR, 0.53 [95% CI, 0.45–0.62]), or any CVD prevention medication (OR, 0.62 [95% CI, 0.52–0.73]). Women with established CVD, however, had better BP control (OR, 1.31 [95% CI, 1.14–1.50]) but less well-controlled low-density lipoprotein cholesterol (OR, 0.66 [95% CI, 0.57–0.76]), and were less likely to smoke (OR, 13.89 [95% CI, 11.24–17.15]) and achieve physical activity targets (OR, 1.92 [95% CI, 1.61–2.29]). Conversely, women with high CVD risk were less likely than men to have their BP, low-density lipoprotein cholesterol, and bodyweight controlled (OR, 0.46 [95% CI, 0.38–0.55]; OR, 0.60 [95% CI, 0.52–0.69]; OR, 0.55 [95% CI, 0.48–0.63], respectively), despite a higher use of BP-lowering medications (OR, 1.21 [95% CI, 1.01–1.45]). Younger patients (<65 years) with established CVD were less likely to be taking CVD preventive medications, but there were no sex differences by area of residence or education level.

CONCLUSIONS: Large and variable gaps in primary and secondary CVD prevention exist in China, particularly for women. Effective CVD prevention requires an improved overall nationwide strategy and a special emphasis on women with established CVD, who have the greatest disparity and the most to benefit.

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Clinical Perspective

What Is New?

- Chinese women with high cardiovascular disease (CVD) risk, in comparison with men, are less likely to achieve desirable levels of blood pressure, lipid, and body weight control for primary prevention, and women with established CVD are less likely to be using specific guideline-directed medications for secondary prevention.
- Overall, younger women (<65 years) receive the least preventive care, whereas rural women have worse risk factor control than those residing in other locations.
- Level of education was not associated with sex differences in primary or secondary CVD prevention for men or women.

What Are the Clinical Implications?

- Clear sex inequities for both primary and secondary CVD prevention are highlighted in China, with further studies required to understand the contributing and mitigating factors.
- Multifaceted interventions are likely to be needed to improve awareness, empowerment, and the ability of individuals to optimize CVD prevention.

Cardiovascular disease (CVD), including coronary heart disease and stroke, accounts for 26.6% and 27.4% of deaths among women and men, globally.[1] In China, however, CVD claims an even higher proportion of loss of life in women (38.9%) and men (35.5%).[1] Prevention is key for patients with established CVD and those at high risk of future CVD events. Risk factor control through evidence-based drug therapy and healthy behaviors are well-recognized cost-effective strategies for reducing CVD risk by up to 80%.[1–11]

Despite improvements in diagnostic and therapeutic interventions to combat CVD in recent decades, significant variations in its prevention according to sex and other sociodemographic characteristics persist across the globe. In particular, it is recognized that women are less likely to be screened for CVD in primary care,[12] have fewer interventions (percutaneous coronary intervention or coronary artery bypass grafting) at the time of myocardial infarction,[13–15] and are less likely to be prescribed intensive statin therapy after a CVD event, in comparison with men.[16,17] These factors contribute to an excess mortality from CVD in women in comparison with men,[18] particularly in rural and remote regions.[19,20]

In China, guideline-recommended CVD preventive medication use and risk factor control are suboptimal,[21,22] but few data exist on sex differences in CVD prevention and long-term management in this massive population. Herein, we describe sex differences in the primary and secondary prevention of CVD in community-dwelling people, and assess any interaction with age, education, residence, and level of affluence or disadvantage.

METHODS

Study Design

A 2-stage, stratified cluster design was used to obtain a representative sample of adults (aged ≥45 years) in the general population, covering 7 geographic regions of China (Northeast, North, Northwest, East, Central, South, and Southwest China). A computer program randomly selected Beijing, the Xinjiang Uyghur Autonomous Region, and the provinces of Henan, Jilin, Guangdong, Yunnan, Jiangxi, and Zhejiang for further sampling. From each city or province, the aim was to survey 4000 residents (living in the area for >6 months) in both urban and rural areas, with 1 to 3 representative communities included in a capital city and 1 to 13 representative villages in a rural area. Accompanied by the administrative staff of a local community or village, trained research staff undertook door-to-door surveys of the community, visiting each home up to 3 times at different times to identify potentially eligible participants. The study was conducted from June 1, 2014, to December 31, 2016; the distribution of study sites is shown in Figure I in the online-only Data Supplement. The ethics committee of Beijing Anzhen Hospital approved the study, and written informed consent was obtained from each participant. The data, methods used in analyses, and materials used in the conduct of the research will be made available to researchers for the purposes of reproducing the results upon formal request to the corresponding author.

Data Collection

We invited all eligible individuals to participate in the survey and to undergo a physical examination with laboratory testing at local community centers. Trained research staff administered a standard questionnaire to obtain data on sociodemographics (age, sex, marital status, level of education, household income, health insurance), health behaviors (tobacco use, diet measured by qualitative food frequency questionnaire, physical activity measured by the Global Physical Activity Questionnaire,[23] and alcohol consumption), and self-reported medical history, including that related to CVD (coronary heart disease, stroke/transient ischemic attack, heart failure, and atrial fibrillation); these data were recorded on a purpose-built electronic data capture system that included range and logic checks, and controls for missing data. Quality assurance staff also reviewed the accumulating data. CVD risk factors (hypertension, dyslipidemia, and diabetes mellitus) were assessed by self-reported physician diagnosis, risk factor–related medication use, or abnormal levels directly measured in the study. Participants also had all their regular medicines checked and recorded.

Definitions

CVD was defined as a history of coronary heart disease (self-report of myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting), or stroke

(self-report of stroke/ transient ischemic attack, or presence of any consistent focal neurological deficit).

Ten-year CVD (nonfatal myocardial infarction, fatal or nonfatal stroke, and CVD death) risk was estimated according to the PAR CVD risk model (Prediction for ASCVD Risk in China),[24] as recommended in the Chinese CVD prevention guidelines.[25] High risk was defined as a predicted 10-year CVD risk ≥10%. Factors used in the risk prediction model were: age, mean values of ≥2 systolic BP measures; fasting total cholesterol, high-density lipoprotein cholesterol, current smoking (yes/no), and diabetes mellitus (yes/no), body mass index (BMI), waist circumference, geographic region (northern/southern China), resident at urban/rural area, and family history of CVD. Smoking status was defined as self-reported nonsmoker, former smoker (≥1 year), or current smoker. Diabetes mellitus was defined as a fasting blood glucose ≥7.0 mmol/L, taking antidiabetic medicines, or having a previous postprandial blood glucose ≥11.1 mmol/L, hemoglobin A1c ≥7%, or diagnosis of diabetes mellitus. Cholesterol and blood glucose were measured at a central laboratory certified by the College of American Pathologists (GuangZhou Kingmed Testing Science & Technology Co, Ltd). Bodyweight, height, and waist circumference were measured by trained study personnel using standard methods. Beijing, the Xinjiang Uyghur Autonomous Region, and the Henan and Jilin provinces were defined as northern China, whereas the provinces of Guangdong, Yunnan, Jiangxi, and Zhejiang were defined as southern China. Family history of CVD was defined as any parent or lineal brother or sister of a participant had a history of coronary heart disease or stroke.

Hypertension was defined as measured systolic BP ≥140 mm Hg, diastolic BP ≥90 mm Hg, taking antihypertensive medication, or self-report of a previous diagnosis of hypertension. Dyslipidemia was defined as total cholesterol ≥240 mg/dL, low-density lipoprotein cholesterol (LDL-C) ≥160 mg/dL, taking a statin or other lipid-lowering agent, or a previous diagnosis of dyslipidemia.

Participants were asked about the use of antiplatelet agents (aspirin or clopidogrel), lipid-lowering drugs (statins or other lipid-lowering agents), and BP-lowering drugs (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, diuretics, β-blockers, and calcium channel antagonists). Open-ended questions were used to capture additional medications, not specifically listed.

We evaluated whether participants had their risk factors controlled according to variable reference categories: BP <130/80 mm Hg; LDL-C <2.6 mmol/L; not a current smoker; BMI between 18.5 and 24.0 kg/m^2; and achieving physical activity targets, defined as ≥30 minutes of moderate-intensity leisure-time physical activity on ≥5 days per week or ≥20 minutes of vigorous-intensity leisure-time physical activity on ≥3 days every week, according to the guidelines.[23]

Statistical Methods

The overall use of primary and secondary CVD preventive medications and level of risk factor control were estimated in those with either established CVD or at high 10-year risk (≥10%) of CVD, in women and men. Prevalence estimates were generated by the SAS PROC SURVEYFREQ procedure, incorporating 3 steps of adjustment (sampling weighting, nonresponse weighting, and population weighting). Data from the China Population Census in 2010 were used as the standard reference population to calculate weighted prevalence. Categorical variables are shown as n (%), and continuous variables are shown as mean (SD). To account for missing data, we assigned corresponding means and reference groups to the missing continuous and categorical covariates, respectively. Continuous variables were compared by using the unpaired *t* test, categorical variables by using the χ^2 test. Associations between sex and drug use, and CVD risk factor control, were evaluated using the SAS PROC SURVEYLOGISTIC procedure, with adjustment for sociodemographic and clinically relevant covariates, including age, sex, area of residence (urban versus rural), region, education level, household income, insurance status, occupation, and history of diabetes mellitus, dyslipidemia, hypertension, and heart failure, based on previous reports.[21] Heterogeneity of associations was tested between different subgroups (age, <65 versus ≥65 years; resident, urban versus rural; education level, lower than college versus college or higher) by adding an interaction term into the regression model. Data are reported as adjusted odds ratios (ORs) with 95% CIs for women, versus men as the reference. A 2-sided *P* value <0.05 was considered statistically significant. All analyses were conducted using SAS software (version 9.4).

RESULTS

A total of 64 893 people were invited to participate from 39 communities (14 urban and 25 rural), and 47 841 (73.7%) completed the survey; response rates were 66.4% and 79.3% in men and women, and of 80.3% and 69.0% in rural and urban residents, respectively (Table I in the online-only Data Supplement). Some 47 625 and 42 894 people had BP measurements and laboratory testing, respectively. The Table shows that 61.3% of responders were women (age 59.8±9.6 years) and 38.7% were men (age 61.4±9.7 years); 5454 (57.2% women) had established CVD, 9532 (70.5% women) had a high estimated 10-year CVD risk (≥10%), and the remaining 32 855 (71.3% women) were identified as having a low estimated 10-year CVD risk (<10%).

In comparison with men, women were less likely to receive higher education (college and above), to have higher household income (annual household income ≥30 000 Chinese Yuan Renminbi [~US dollars 4260]), more likely to be widowed (30.1% versus 8.6% in the high CVD risk group, 22.2% versus 6.5% in established CVD group), or have a history of dyslipidemia (25.2% versus 16.7% in the high CVD risk group, 34.2% versus 31.3% in established CVD group), and less likely to be current smokers or habitual drinkers. More women had a history of hypertension (56.6% versus 41.7%) or diabetes mellitus (34.8% versus 15.1%) in the high CVD risk group, whereas fewer women reported a history of hypertension (51.7% versus 54.8%); a similar proportion of women and men had a history of diabetes

Table. Characteristics of Participants With and Without Established Cardiovascular Disease, by Sex

Characteristics	Low and Medium Estimated 10-Year CVD Risk Without Established CVD n=32 855			High Estimated 10-Year CVD Risk Without Established CVD n=9532			With Established CVD n=5454		
	Women n=23 415	Men n=9440	*P* Value	Women n=2811	Men n=6721	*P* Value	Women n=3120	Men n=2334	*P* Value
Age, mean (SD), y	58.0 (8.7)	56.0 (7.0)	<0.0001	71.2 (8.3)	67.9 (8.7)	<0.0001	63.2 (9.6)	64.9 (9.3)	<0.0001
Rural residents, n (%)	10 695 (45.7)	4639 (49.1)	<0.0001	1106 (39.3)	3370 (50.1)	<0.0001	1146 (36.7)	854 (36.6)	0.92
Race, n (%)									
Han nationality	22 264 (95.1)	8981 (95.1)	0.84	2669 (94.9)	6446 (95.9)	0.037	2917 (93.5)	2181 (93.4)	0.94
Non-Han nationality	1151 (4.9)	459 (4.9)		142 (5.1)	275 (4.1)		203 (6.5)	153 (6.6)	
Education level, n (%)									
Middle school and below	19 588 (83.7)	7588 (80.4)	<0.0001	2427 (86.3)	5458 (81.2)	<0.0001	2634 (84.4)	1844 (79)	<0.0001
College and above	3827 (16.3)	1852 (19.6)		384 (13.7)	1263 (18.8)		486 (15.6)	490 (21.0)	
Marital status, n (%)									
Married	20 190 (86.2)	8984 (95.2)	<0.0001	1954 (69.5)	6034 (89.8)	<0.0001	2373 (76.1)	2137 (91.6)	<0.0001
Unmarried/divorced/ separated	535 (2.3)	231 (2.4)		11 (0.4)	108 (1.6)		56 (1.8)	45 (1.9)	
Widowed	2690 (11.5)	225 (2.4)		846 (30.1)	579 (8.6)		691 (22.2)	152 (6.5)	
Occupation, n (%)									
Manual laborer	15 547 (66.4)	6090 (64.5)	0.0011	2059 (73.2)	4713 (70.1)	0.002	2161 (69.3)	1587 (68.0)	0.32
Nonmanual laborer	7868 (33.6)	3350 (35.5)		752 (26.8)	2008 (29.9)		959 (30.7)	747 (32.0)	
Health insurance, n (%)									
Other	463 (3.6)	234 (4.3)	<0.0001	72 (5.4)	116 (3.5)	0.01	77 (4.3)	50 (3.5)	0.002
New Rural Cooperative Medical Scheme	10 046 (42.9)	3789 (40.1)		1401 (49.8)	3268 (48.6)		1267 (40.6)	846 (36.2)	
Urban employees/ residence insurance	12 906 (55.1)	5417 (57.4)		1338 (47.6)	3337 (49.7)		1776 (56.9)	1438 (61.6)	
Annual household income, n (%)									
<¥ 30 000*	8740 (37.3)	2846 (30.1)	<0.0001	1341 (47.7)	2777 (41.3)	<0.0001	1393 (44.6)	902 (38.6)	<0.0001
≥¥ 30 000	14 675 (62.7)	6594 (69.9)		1470 (52.3)	3944 (58.7)		1727 (55.4)	1432 (61.4)	
Smoking status, n (%)									
Noncurrent smoker	22 515 (96.2)	4704 (49.8)	<0.0001	2510 (89.3)	4037 (60.1)	<0.0001	2920 (93.6)	1469 (62.9)	<0.0001
Current smoker	900 (3.8)	4736 (50.2)		301 (10.7)	2684 (39.9)		200 (6.4)	865 (37.1)	
Drinking status, n (%)									
Nonhabitual drinker	21 539 (92)	5612 (59.4)	<0.0001	2653 (94.4)	4507 (67.1)	<0.0001	2885 (92.5)	1649 (70.7)	<0.0001
Habitual drinker	1876 (8.0)	3828 (40.6)		158 (5.6)	2214 (32.9)		235 (7.5)	685 (29.3)	
Heart failure, n (%)	105 (0.4)	23 (0.2)	0.007	26 (0.9)	48 (0.7)	0.29	124 (4.0)	103 (4.4)	0.42
Dyslipidemia, n (%)	3962 (16.9)	1236 (13.1)	<0.0001	707 (25.2)	1121 (16.7)	<0.0001	1067 (34.2)	730 (31.3)	0.023
Hypertension, n (%)	5851 (25.0)	1651 (17.5)	<0.0001	1592 (56.6)	2801 (41.7)	<0.0001	1612 (51.7)	1279 (54.8)	0.022
Diabetes mellitus, n (%)	1340 (5.7)	471 (5.0)	0.008	979 (34.8)	1015 (15.1)	<0.0001	597 (19.1)	444 (19.0)	0.92

Data are expressed as number (%) or mean (SD). CVD indicates cardiovascular disease; and USD, US dollars.
*¥ 30 000 equals USD4260.

mellitus (19.1% versus 19.0%) in those with established CVD (Table).

Sex Difference in CVD Primary Prevention for High-Risk Individuals

In general, the proportion of primary prevention drug use was low in both sexes, with the use of BP-lowering, lipid-lowering, and antiplatelet drugs being 44.4%, 10.2%, and 13.2% in women and 36.3%, 6.3%, and 8.1% in men, respectively, in the high CVD risk group for primary prevention. Only 48.5% of women and 39.3% of men were taking at least one guideline-recommended medication. Despite being more likely to be treated with BP-lowering drugs (OR, 1.21 [95% CI, 1.01–1.45]), women were less likely to have their

modifiable risk factors controlled, with 54%, 40%, and 45% lower odds of meeting BP, LDL-C, and BMI targets, respectively. Conversely, women had a 380% higher odds of being a nonsmoker, and a 29% higher odds of meeting physical activity targets (Figure 1).

Sex Difference in CVD Secondary Prevention for Individuals With Established CVD

Secondary preventive medicine use in women was consistently less frequent than that in men; only 39.5%, 16.4%, and 20.9% of women, in comparison with 46.7%, 22.5%, and 34.2% of men, were using BP-lowering, lipid-lowering, and antiplatelet drugs, respectively. Moreover, 48.6% of women, in comparison with 59.8% of men, were taking at least one guideline-recommended medication. The odds of women taking BP-lowering, lipid-lowering, and antiplatelet drugs, and any indicated drugs, in comparison with men, were 0.79 (95% CI, 0.65–0.95), 0.69 (95% CI, 0.56–0.84), 0.53 (95% CI, 0.45–0.62), and 0.62 (95% CI, 0.52–0.73), respectively (Figure 1).

With respect to CVD risk factor control, women with established CVD were more likely to have adequate BP control (35.2% of women versus 28.7% of men, OR, 1.31 [95% CI, 1.14–1.50]) but less likely to meet the recommended LDL-C target (27.5% of women versus 38.2% of men, OR, 0.66 [95% CI, 0.57–0.76]). A greater proportion of women were nonsmokers (95.1% versus 64.7%, OR, 13.89 [95% CI, 11.24–17.15]) and achieved physical activity targets (86.6% versus 77.0%, OR, 1.92 [95% CI, 1.61–2.29]).

Sex differences in medication use and risk factor control were significantly different in primary and secondary CVD prevention (all $P_{\text{for interaction}} \leq 0.001$ except in achieving LDL-C target (Figure 1).

Sex Differences in CVD Prevention, by Age, by Rurality, and by Education

In comparison with older women (aged ≥65 years), sex disparities in those at high CVD risk at a younger age (<65 years) were significantly higher in the use of antiplatelets (OR, 0.58 [95% CI, 0.39–0.88], and 1.20 [95% CI, 0.92–1.56]; $P_{\text{for interaction}}=0.0005$), whereas sex disparities favored younger women in having well-controlled BP (OR, 0.87 [95% CI, 0.55–1.36] and OR, 0.49 [95% CI, 0.40–0.59]; $P_{\text{for interaction}}=0.0002$) and achieving the physical activity goal (OR, 4.18 [95% CI, 2.98–5.86] and OR, 1.43 [95% CI, 1.22–1.67]; $P_{\text{for interaction}}<0.0001$; Figure 2). Disparities in younger women who received even fewer CVD medications were more obvious and consistent for secondary prevention, whereas sex disparities favored younger women in having well-controlled BP (OR, 1.73 [95% CI, 1.44–2.07] in those <65 years and OR, 0.99 [95% CI, 0.80–1.22] in those ≥65 years; $P_{\text{for interaction}}=0.0002$), being a nonsmoker (OR, 14.36 [95%CI, 11.24–18.36] in those <65 years and OR, 9.25 [95% CI 6.57–13.02] in those ≥65 years; $P_{\text{for interaction}}=0.02$), and achieving the physical activity goal (OR, 2.69 [95% CI, 2.12–3.41] in those <65 years,

Medication use	CVD prevention	Women (%)	Men (%)	Odds ratio (95%CI)	P for interaction
Any BP-lowering drugs	Primary	44.4	36.3	1.21 (1.01-1.45)	
	Secondary	39.5	46.7	0.79 (0.65-0.95)	<0.0001
Any lipid-lowering drugs	Primary	10.2	6.3	1.02 (0.78-1.34)	
	Secondary	16.4	22.5	0.69 (0.56-0.84)	<0.0001
Any antiplatelets	Primary	13.2	8.1	0.98 (0.78-1.24)	
	Secondary	20.9	34.2	0.53 (0.45-0.62)	<0.0001
Any drug use*	Primary	48.5	39.3	1.14 (0.95-1.37)	
	Secondary	48.6	59.8	0.62 (0.52-0.73)	<0.0001
Risk factor control					
BP<130/80mmHg	Primary	11.4	15.7	0.46 (0.38-0.55)	
	Secondary	35.2	28.7	1.31 (1.14-1.50)	<0.0001
LDL-C<2.6mmol/l	Primary	21.7	29.0	0.60 (0.52-0.69)	
	Secondary	27.5	38.2	0.66 (0.57-0.76)	0.47
Normal weight	Primary	23.1	37.4	0.55 (0.48-0.63)	
	Secondary	36.2	34.4	0.98 (0.85-1.13)	<0.0001
Not a current smoker	Primary	91.5	62.7	4.80 (4.07-5.65)	
	Secondary	95.1	64.7	13.89 (11.24-17.15)	<0.0001
Achieving physical activity targets	Primary	80.0	73.6	1.29 (1.10-1.50)	
	Secondary	86.6	77.0	1.92 (1.61-2.29)	0.0003

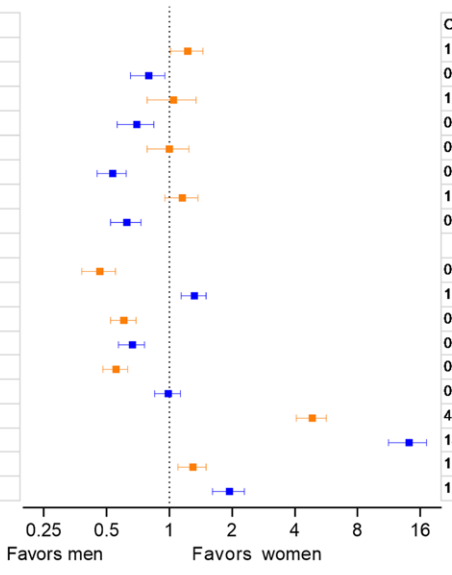

Figure 1. Adjusted sex differences in CVD primary and secondary prevention.
Adjusted odds ratios (OR, 95% CI) of women vs men to evaluate the association between sex and individual medication use (antiplatelet, lipid-lowering drug, BP-lowering drug), any drug use, and the achievement of individual risk factor control targets. Men served as the reference group. Age, region (rural, urban), province, education level, occupation, health insurance, annual household income, and comorbidities (heart failure, dyslipidemia, hypertension, diabetes mellitus) were included in the adjustment. Dyslipidemia and hypertension are not included, respectively, in adjustment for risk factor control targets of LDL-C and blood pressure. *Any antiplatelets, any lipid-lowering drugs, or any BP-lowering drugs. BP indicates blood pressure; CVD, cardiovascular disease; and LDL-C, low-density lipoprotein cholesterol.

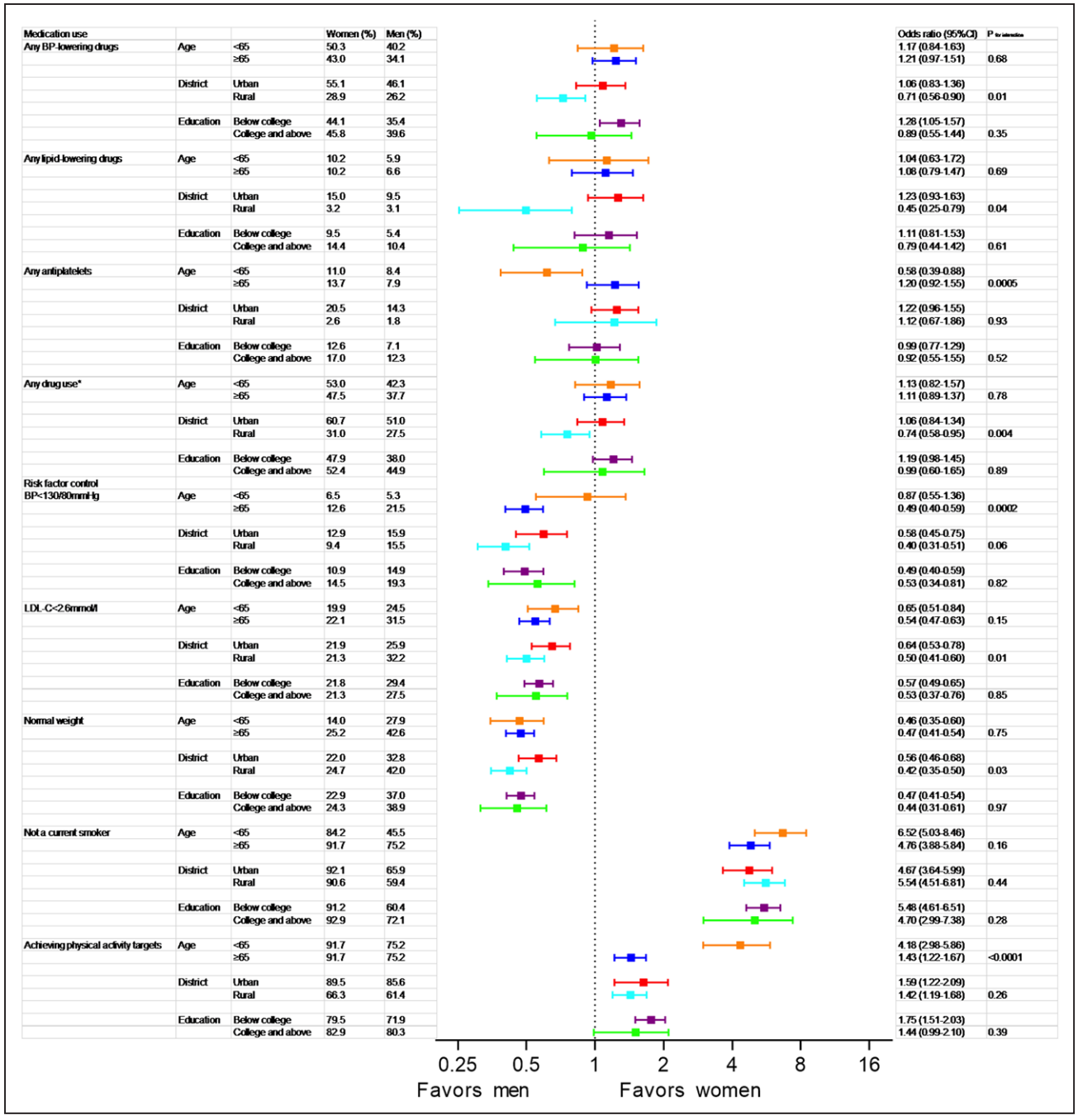

Figure 2. Adjusted sex differences in CVD primary prevention, by age, rurality, and education level for participants with high 10-year CVD risk. Subgroup analysis to evaluate the interaction between sex disparities and age, rurality, and education level, respectively, in CVD primary prevention; expressed as adjusted OR (95% CI) of women vs men in individual medication use (BP-lowering drug, lipid-lowering drug, antiplatelet drug, and any drug use), and individual risk factor control target achievement. Men served as the reference group. Age, region (rural, urban), province, education level, occupation, health insurance, annual household income, comorbidities (heart failure, dyslipidemia, hypertension, diabetes mellitus) were included in the adjustment. Age, region (rural, urban), and education level were not included, respectively, in the evaluation of the interaction between these factors and sex disparities. Dyslipidemia and hypertension are not included, respectively, in adjustment for the risk factor control targets of LDL-C and blood pressure. *Any antiplatelets, any lipid-lowering drugs, or any BP-lowering drugs. BP indicates blood pressure; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; and OR, odds ratio.

and OR, 1.47 [95% CI 1.15–1.89] in those ≥65 years; $P_{\text{for interaction}}$=0.0002) (Figure 3).

Rural residents demonstrated particularly poor primary CVD prevention, especially with respect to the use of preventive medications. In comparison with their urban counterparts, sex disparities were larger in the use of BP-lowering drugs (OR, 0.71 [95% CI, 0.56–0.90] in rural residents and OR. 1.06 [95% CI, 0.83–1.36] in urban residents; $P_{\text{for interaction}}$=0.01), lipid-lowering drugs (OR, 0.45 [95% CI, 0.25–0.79] in rural residents and OR, 1.23 [95% CI, 0.93–1.63] in urban residents; $P_{\text{for interaction}}$=0.04), achieving LDL-C targets

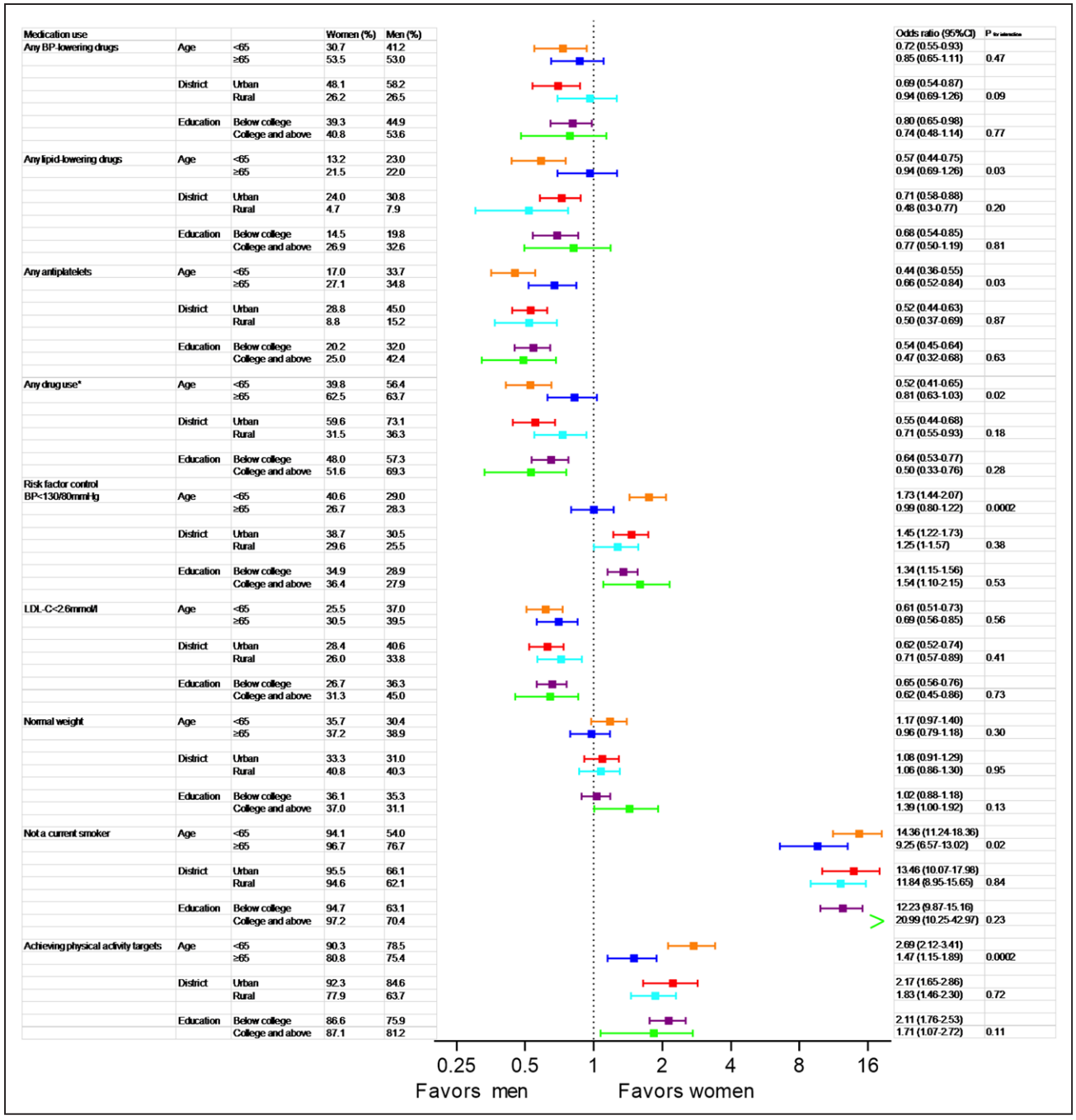

Figure 3. Adjusted sex differences in CVD secondary prevention, by age, rurality, and education level for participants with established CVD.
Subgroup analysis to evaluate the interaction between sex disparities and age, rurality, and education level, respectively, in CVD secondary prevention; expressed as adjusted OR (95%CI) of women vs men in individual medication use (BP-lowering drug, lipid-lowering drug, antiplatelet, and any drug use), and individual risk factor control target achievement. Men served as the reference group. Age, region (rural, urban), province, education level, occupation, health insurance, annual household income, and comorbidities (heart failure, dyslipidemia, hypertension, diabetes mellitus) were included in the adjustment. Age, region (rural, urban), and education level were not included, respectively, in the evaluation of the interaction between these factors and sex disparities. Dyslipidemia and hypertension are not included, respectively, in adjustment for the risk factor control targets of LDL-C and blood pressure. *Any antiplatelets, any lipid-lowering drugs, or any BP-lowering drugs. BP indicates blood pressure; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; and OR, odds ratio.

(OR, 0.50 [95% CI, 0.41–0.60] in rural residents, and OR, 0.64 [95% CI, 0.53–0.78] in urban residents; $P_{\text{for interaction}}$=0.01), and keeping BMI within normal range (OR, 0.42 [95% CI, 0.35–0.50] in rural residents, and OR, 0.56 [95% CI, 0.46–0.68] in urban residents; $P_{\text{for interaction}}$=0.03; Figure 2). For CVD secondary prevention, sex disparities were not significantly different between rural and urban residents with respect to either preventive drug therapies or in achieving optimal risk factor control (Figure 3).

Higher education status was associated with better primary and secondary CVD prevention profiles in both

women and men, but sex disparities were not different according to education level for both primary and secondary CVD prevention (Figures 2 and 3).

DISCUSSION

This is the first study to quantify the uptake of primary and secondary CVD prevention strategies in urban and rural China through a sex lens. In providing contemporary sex comparisons in a sample of 9552 individuals with high 10-year CVD risk and 5454 individuals with established CVD in Chinese community-based settings, the study shows the existence of grossly suboptimal overall primary and secondary CVD prevention. In comparison with men, women with established CVD are less likely to be using guideline-directed secondary prevention medications, and those at high CVD risk are less likely to achieve BP, LDL-C, and body weight control. These findings are largely consistent across different age groups, residential areas, and level of education. Of particular note is that younger women received the least preventive care, and rural women had the worst level of risk factor control in comparison with those in other locations. However, education level was not associated with sex differences in primary or secondary CVD prevention.

Our findings indicate a pressing need for better development of CVD prevention in China. The current primary healthcare system appears to be ineffective at controlling CVD risk factors in those at highest risk, whereas hospitals focusing on treating acute diseases are ignoring long-term disease management and prevention in those with established CVD.[26] Differences in health insurance coverage could help explain some of the disparities in CVD prevention. Although the majority of the rural population (95%) have joined the New Rural Cooperative Medical Scheme, this only provides cover for in-hospital costs, and the requirement for long-term BP-lowering medications, statins, and antiplatelet agents require out-of-pocket payment.[27] Conversely, urban residents usually hold Urban Employee/Resident Insurance that provides some coverage (70%) of outpatient medication and over-the-counter costs for CVD prevention. This lack of insurance coverage is an important missed opportunity in CVD prevention given the increasing evidence showing that >75% of the CVD burden could potentially be reduced by controlling metabolic and behavioral risk factors.[10,28]

Disadvantaged populations experience the greatest CVD burden and socioeconomic inequalities between women and men, amplifying disparities in CVD risk factor control. It has been reported that sex inequalities in individual incomes appear to make a large contribution to the poor health of women.[29] Although disparities have been observed in the acute care of patients with CVD,[22,26,30] data are scarce regarding sex differences in CVD prevention in the massive Chinese population. Because of different health care–seeking behaviors, physicians' sex bias, and different prevalence of CVD risk factors,[31] the profiles of drug therapies and risk factors control in women and men are very different. For women, more attention needs to be paid on lipid control, whereas, for men, smoking and a sedentary lifestyle are the 2 most prevalent CVD risk factors to be addressed, both in primary prevention and secondary prevention.

Understanding the reasons for the observed sex differences is crucial to inform current policy development in China. Our study showed that women, in comparison with men, are 20% to 50% less likely to receive guideline-directed therapies after a diagnosis of CVD. We identified that young women were at particular risk of suboptimal secondary prevention. This may reflect bias within the healthcare system, with low awareness at the physician level that CVD can affect young women. The disparities between women and men were not reduced in urban residents and in those with a high education in our study, suggesting that sex disparities could not be attributed to economic development or general education alone.

CVD secondary prevention medication underuse and poor risk factor control is an issue at a global level, especially in low-middle income countries and rural areas, as indicated in a multinational community study undertaken between 2003 and 2009.[21] Our findings extend previous data from Western countries highlighting that women are less likely to receive guideline-recommended therapy.[13,16,18,32] Gaps and disparities found in our study could give insightful guidance for future interventions, including but not limited to conducting more studies to determine reasons for sex inequities in both primary and secondary prevention, implementing multifaceted interventions to improve patient awareness, empowerment, and self-care ability, embracing polypill strategies, enhancing general practitioner skills and primary care networks for community dwellers.

This study has several important strengths, including its novelty, because there are few data, to the best of our knowledge, concerning sex differences in CVD prevention and management in China. This recent well-conducted national epidemiological study provides useful new data for individuals from both urban and rural communities in China, allowing us to insightfully analyze sex differences in CVD primary and secondary prevention. CVD studies conducted in hospital, clinic, or other settings where patients are followed up by general practitioners, usually lead to an overestimation of secondary preventative medication use and risk factor control. We believe this bias has been minimized in our community-based design. Even so, our study has several limitations. First, although the provinces were randomly selected, the communities and villages were not, raising potential for selection bias. Second, although a

response rate of 75% is generally considered reasonable, the characteristics of nonresponders might be different from responders. For example, as a consequence of people with limited access to health care being more likely to respond to our invitation, those who did not respond might have had a better profile of risk factor control and use of preventative drugs. Moreover, the lower response in men (66.4%) in comparison with women (79.3%) might have led to an underestimation or overestimation of the sex disparities in adopting preventive health care. Last, despite our efforts to restrict the diagnosis of CVD to having a history of myocardial infarction or stroke, or ever receiving percutaneous coronary intervention or coronary artery bypass grafting therapy, we acknowledge potential misclassification bias from the use of a self-reported questionnaire despite high public awareness of these conditions in China.[33]

Conclusions

Despite nationwide efforts to combat CVD, both primary and secondary CVD prevention remain suboptimal in China across both sexes. Our study has shown large differences in primary and secondary CVD prevention profiles between women and men, most notably for women with established CVD being less likely to be taking guideline-directed medications, and those at high CVD risk being less likely than men to have their BP, LDL-C, or BMI well controlled. Effective strategies for CVD prevention in both men and women, with special emphasis on women, are urgently required to improve the health of this large population.

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REFERENCES

1. Hackam DG, Spence JD. Combining multiple approaches for the secondary prevention of vascular events after stroke: a quantitative modeling study. *Stroke.* 2007;38:1881–1885. doi: 10.1161/STROKEAHA.106.475525
2. Kerr AJ, Broad J, Wells S, Riddell T, Jackson R. Should the first priority in cardiovascular risk management be those with prior cardiovascular disease? *Heart.* 2009;95:125–129. doi: 10.1136/hrt.2007.140905
3. Briffa TG, Hobbs MS, Tonkin A, Sanfilippo FM, Hickling S, Ridout SC, Knuiman M. Population trends of recurrent coronary heart disease event rates remain high. *Circ Cardiovasc Qual Outcomes.* 2011;4:107–113. doi: 10.1161/CIRCOUTCOMES.110.957944
4. Hankey GJ. Secondary stroke prevention. *Lancet Neurol.* 2014;13:178–194. doi: 10.1016/S1474-4422(13)70255-2
5. De Smedt D, Kotseva K, De Bacquer D, Wood D, De Backer G, Dallongeville J, Seppo L, Pajak A, Reiner Z, Vanuzzo D, et al. Cost-effectiveness of optimizing prevention in patients with coronary heart disease: the EUROASPIRE III health economics project. *Eur Heart J.* 2012;33:2865–2872. doi: 10.1093/eurheartj/ehs210
6. Yusuf S. Two decades of progress in preventing vascular disease. *Lancet.* 2002;360:2–3. doi: 10.1016/S0140-6736(02)09358-3
7. Gouya G, Arrich J, Wolzt M, Huber K, Verheugt FW, Gurbel PA, Pirker-Kees A, Siller-Matula JM. Antiplatelet treatment for prevention of cerebrovascular events in patients with vascular diseases: a

systematic review and meta-analysis. *Stroke.* 2014;45:492–503. doi: 10.1161/STROKEAHA.113.002590
8. Ma TT, Wong ICK, Man KKC, Chen Y, Crake T, Ozkor MA, Ding LQ, Wang ZX, Zhang L, Wei L. Effect of evidence-based therapy for secondary prevention of cardiovascular disease: systematic review and meta-analysis. *PLoS One.* 2019;14:e0210988. doi: 10.1371/journal.pone.0210988
9. Mok Y, Sang Y, Ballew SH, Rebholz CM, Rosamond WD, Heiss G, Folsom AR, Coresh J, Matsushita K. American Heart Association's Life's Simple 7 at middle age and prognosis after myocardial infarction in later life. *J Am Heart Assoc*. 2018;7:e007658.
10. O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, Rao-Melacini P, Zhang X, Pais P, Agapay S, et al; INTERSTROKE investigators. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet.* 2016;388:761–775. doi: 10.1016/S0140-6736(16)30506-2
11. Park JH, Ovbiagele B. Optimal combination secondary prevention drug treatment and stroke outcomes. *Neurology.* 2015;84:50–56. doi: 10.1212/WNL.0000000000001099
12. Hyun KK, Redfern J, Patel A, Peiris D, Brieger D, Sullivan D, Harris M, Usherwood T, MacMahon S, Lyford M, et al. Gender inequalities in cardiovascular risk factor assessment and management in primary healthcare. *Heart.* 2017;103:492–498. doi: 10.1136/heartjnl-2016-310216
13. Worrall-Carter L, McEvedy S, Wilson A, Rahman MA. Gender differences in presentation, coronary intervention, and outcomes of 28,985 acute coronary syndrome patients in Victoria, Australia. *Womens Health Issues.* 2016;26:14–20. doi: 10.1016/j.whi.2015.09.002
14. Worrall-Carter L, MacIsaac A, Scruth E, Rahman MA. Gender difference in the use of coronary interventions for patients with acute coronary syndrome: Experience from a major metropolitan hospital in Melbourne, Australia. *Aust Crit Care.* 2017;30:3–10. doi: 10.1016/j.aucc.2016.03.005
15. Khan E, Brieger D, Amerena J, Atherton JJ, Chew DP, Farshid A, Ilton M, Juergens CP, Kangaharan N, Rajaratnam R, et al. Differences in management and outcomes for men and women with ST-elevation myocardial infarction. *Med J Aust.* 2018;209:118–123.
16. Peters SAE, Colantonio LD, Zhao H, Bittner V, Dai Y, Farkouh ME, Monda KL, Safford MM, Muntner P, Woodward M. Sex differences in high-intensity statin use following myocardial infarction in the United States. *J Am Coll Cardiol.* 2018;71:1729–1737. doi: 10.1016/j.jacc.2018.02.032
17. Nanna MG, Wang TY, Xiang Q, Goldberg AC, Robinson JG, Roger VL, Virani SS, Wilson PWF, Louie MJ, et al. Sex differences in the use of statins in community practice. *Circ Cardiovasc Qual Outcomes.* 2019;12:e005562. doi: 10.1161/CIRCOUTCOMES.118.005562
18. Bots SH, Peters SAE, Woodward M. Sex differences in coronary heart disease and stroke mortality: a global assessment of the effect of ageing between 1980 and 2010. *BMJ Glob Health.* 2017;2:e000298. doi: 10.1136/bmjgh-2017-000298
19. Lindroth M, Lundqvist R, Lilja M, Eliasson M. Cardiovascular risk factors differ between rural and urban Sweden: the 2009 Northern Sweden MONICA cohort. *BMC Public Health.* 2014;14:825. doi: 10.1186/1471-2458-14-825
20. Yan R, Li W, Yin L, Wang Y, Bo J, PURE-China Investigators. Cardiovascular diseases and risk-factor burden in urban and rural communities in high-, middle-, and low-income regions of China: a large community-based epidemiological study. *J Am Heart Assoc*. 2017;6: e004445.
21. Yusuf S, Islam S, Chow CK, Rangarajan S, Dagenais G, Diaz R, Gupta R, Kelishadi R, Iqbal R, Avezum A, et al; Prospective Urban Rural Epidemiology (PURE) Study Investigators. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey. *Lancet.* 2011;378:1231–1243. doi: 10.1016/S0140-6736(11)61215-4
22. Chen Y, Li L, Zhang Q, Clarke R, Chen J, Guo Y, Bian Z, Pan X, Peto R, Tao R, et al; China Kadoorie Biobank Study. Use of drug treatment for secondary prevention of cardiovascular disease in urban and rural communities of China: China Kadoorie Biobank Study of 0.5 million people. *Int J Cardiol.* 2014;172:88–95. doi: 10.1016/j.ijcard.2013.12.065
23. Smith SC Jr, Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, Gibbons RJ, Grundy SM, Hiratzka LF, Jones DW, et al; World Heart Federation and the Preventive Cardiovascular Nurses Association. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. *Circulation.* 2011;124:2458–2473. doi: 10.1161/CIR.0b013e318235eb4d
24. Yang X, Li J, Hu D, Chen J, Li Y, Huang J, Liu X, Liu F, Cao J, Shen C, et al. Predicting the 10-year risks of atherosclerotic cardiovascular disease in Chinese population: the China-PAR Project (Prediction for ASCVD Risk in China). *Circulation.* 2016;134:1430–1440. doi: 10.1161/CIRCULATIONAHA.116.022367
25. The Joint Task Force for Guideline on the Assessment and Management of Cardiovascular Risk in China. Guideline on the assessment and management of cardiovascular risk in China. *Chin J Health Manage*. 2019;13:7–29.
26. Du X, Patel A, Anderson CS, Dong J, Ma C. Epidemiology of cardiovascular disease in China and opportunities for improvement: JACC International. *J Am Coll Cardiol.* 2019;73:3135–3147. doi: 10.1016/j.jacc.2019.04.036
27. Gu D, He J, Coxson PG, Rasmussen PW, Huang C, Thanataveerat A, Tzong KY, Xiong J, Wang M, Zhao D, et al. The cost-effectiveness of low-cost essential antihypertensive medicines for hypertension control in China: a modelling study. *PLoS Med.* 2015;12:e1001860. doi: 10.1371/journal.pmed.1001860
28. Pandian JD, Gall SL, Kate MP, Silva GS, Akinyemi RO, Ovbiagele BI, Lavados PM, Gandhi DBC, Thrift AG. Prevention of stroke: a global perspective. *Lancet.* 2018;392:1269–1278. doi: 10.1016/S0140-6736(18)31269-8
29. Malmusi D, Vives A, Benach J, Borrell C. Gender inequalities in health: exploring the contribution of living conditions in the intersection of social class. *Glob Health Action.* 2014;7:23189. doi: 10.3402/gha.v7.23189
30. Hao Y, Liu J, Liu J, Yang N, Smith SC Jr, Huo Y, Fonarow GC, Ge J, Taubert KA, Morgan L, et al. Sex differences in in-hospital management and outcomes of patients with acute coronary syndrome. *Circulation.* 2019;139:1776–1785. doi: 10.1161/CIRCULATIONAHA.118.037655
31. Woodward M. Cardiovascular disease and the female disadvantage. *Int J Environ Res Public Health*. 2019;16: E1165.
32. Zhao M, Vaartjes I, Graham I, Grobbee D, Spiering W, Klipstein-Grobusch K, Woodward M, Peters SA. Sex differences in risk factor management of coronary heart disease across three regions. *Heart.* 2017;103:1587–1594. doi: 10.1136/heartjnl-2017-311429
33. Li S, Cui L-Y, Anderson C, Zhu S, Xu P, Wei T, Luo Y, Chen S, Jiang N, Hong Y, et al. Public awareness of stroke and the appropriate responses in China. *Stroke*. 2019;50:455–462.