

Sex differences in the prevalence of, and trends in, cardiovascular risk factors, treatment, and control in the United States, 2001-2016

Sanne A.E. Peters, PhD^{1,2}, Paul Muntner, PhD³, Mark Woodward, PhD^{1,4,5}

1 The George Institute for Global Health, University of Oxford, Oxford, UK

2 Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands

3 Department of Epidemiology, University of Alabama at Birmingham, Birmingham, Alabama, USA

4 The George Institute for Global Health, University of New South Wales, Sydney, Australia

5 Department of Epidemiology, Johns Hopkins University, Baltimore MD, USA

Running title: Sex differences in trends in CVD risk factors

Correspondence to:

Dr. Sanne Peters

The George Institute for Global Health, University of Oxford

Hayes House, 75 George Street, Oxford, OX1 2BQ, UK

E: sanne.peters@georgeinstitute.ox.ac.uk

Twitter: @saepeters

Abstract

Background: Improvements have been made in the treatment and control of some, but not all, major cardiovascular risk factors in the US. It remains unclear whether women and men have benefited equally.

Methods: Data from the 2001-2002 to 2015-2016 US National Health and Nutrition Examination Survey on adults aged 20 to 79 years were used. We assessed sex differences in temporal trends in the levels of systolic blood pressure (SBP), body mass index (BMI), smoking status, HDL and total cholesterol (TC), and HbA1C. Trends in treatment and control rates of hypertension, diabetes, and dyslipidemia were also assessed.

Results: Overall, 35,416 (51% women) participants were included. Trends in SBP, smoking status, HDL cholesterol, and HbA1C were similar between the sexes. BMI increased more in women than men ($p=0.006$); in 2001-2004 and 2013-2016, mean levels were 28.1 kg/m² and 29.6 kg/m² in women and 27.9 kg/m² and 29.0 kg/m² in men. TC decreased more in men than women ($p=0.002$): mean levels in 2001-2004 and 2013-2016 were 203 and 194 mg/dL in women and 201 and 188 mg/dL in men. Improvements in the control of hypertension, diabetes, and dyslipidemia were similar between the sexes; however, sex differences persisted. In 2013-2016, control rates in women vs. men were 30% vs. 22% for hypertension, 30% vs. 20% for diabetes, and 50% vs. 63% for dyslipidemia.

Conclusions: Temporal trends in cardiovascular risk factor levels were broadly similar between the sexes, except for TC and BMI. Sex differences in the control of hypertension, diabetes, and dyslipidemia persist and further efforts are required to reduce this differential.

Keywords: Sex differences; women; men; cardiovascular disease; risk factors; treatment; risk factor control; prevention

Clinical perspective

What is new?

- Between 2001-2004 and 2013-2016, trends in the reductions in SBP and smoking prevalence and increasing prevalence of diabetes were similar between adult women and men in the United States.
- Reductions in total cholesterol were greater in men than women and increases in BMI were greater in women than men.
- The control of hypertension, diabetes, and dyslipidemia remained suboptimal in both sexes, with a lower prevalence of controlled hypertension and diabetes in men and a lower prevalence of controlled dyslipidemia in women.

What are the clinical implications?

- The presence of clinically meaningful sex differences in the prevalence of, and trends in, cardiovascular risk factors, treatment, and control requires increased awareness in order to improve the prevention of CVD in both women and men.
- Further efforts are particularly required to reduce the persistent sex differences in the control of hypertension, diabetes, and dyslipidemia.
- Sex-specific health promotion efforts may be needed to further reduce smoking rates and to curb the sharp increases in the prevalence of overweight and obesity and diabetes.

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide and accounts for about 1 of every 3 deaths in US women and men.^{1,2} Much of the burden of CVD can be avoided by keeping blood pressure, cholesterol, and glucose at healthy levels, avoiding tobacco, and maintaining a healthy weight.^{1,3} Although the contribution of these risk factors to cardiovascular health is well-established, underlying lifestyle factors are imperfect in many individuals and differences exist between women and men. For example, tobacco use is generally more common in men than women and women tend to have more favourable levels of blood pressure and cholesterol.⁴⁻⁷ In contrast, the worldwide prevalence of obesity is higher in women than men.⁸

In addition to a healthy lifestyle, those with hypertension and dyslipidemia receive CVD risk reduction benefits from pharmacological treatment to control their blood pressure and cholesterol levels.¹ To reduce the risk of micro- and macrovascular complications, those with diabetes benefit from pharmacological treatment to control glucose levels, regardless of sex. While several studies have described the US trends in prevalence, treatment, and control rates for hypertension, diabetes, and dyslipidemia, sex-specific results have not been reported consistently.⁹⁻¹²

CVD has long been seen as a condition primarily affecting men. While the age-specific rates of CVD are higher in men than women in most age groups, the actual lifetime risk of CVD is similar for women and men.^{13,14} Furthermore, evidence suggests that CVD rates not only differ between the sexes, but may also differ between age and racial groups within the same sex.¹ In the last several decades, the American Heart Association's (AHA's) Go Red for Women campaign and women-specific guidelines for the prevention of CVD in the US were initiated to increase awareness of sex differences in CVD and the importance of CVD in women.¹⁵⁻¹⁹ However, it is unknown whether these initiatives have had an impact on sex differences in cardiovascular risk factor levels and treatment and control patterns. Moreover, where sex-specific trends have been reported, these were generally not presented for different age and racial groups nor separately for those with and without a history

of CVD.⁹⁻¹² If such differences exist, health promotion efforts should be reformulated to take this into account.

To address these evidence gaps, we used data from the National Health and Nutrition Examination Survey (NHANES) to quantify sex differences in trends in cardiovascular risk factors (blood pressure, cholesterol, HbA1C, weight, and smoking) and the prevalence, treatment, and control of hypertension, diabetes, and dyslipidemia in the United States from 2001 to 2016, overall and by age group, race, and among those with or without a history of CVD.

Methods

In two-year cycles, NHANES enrolls civilian, noninstitutionalized persons living in the US. Participants are selected using a multistage probability sampling approach such that nationally representative estimates can be generated. Data were used from the eight 2-year NHANES cycles conducted between 2001-2002 and 2015-2016. NHANES cycles were combined into four four-year periods (2001-2004, 2005-2008, 2009-2012, 2013-2016) to produce sex-specific estimates with greater statistical reliability.²⁰ The present study included 35,774 adults (51% women) 20-79 years of age at study assessment. The full protocols and methods for data collection are reported elsewhere.²¹ All participants provided written informed consent and the research ethics boards of the National Center for Health Statistics (NCHS) approved all protocols; the data are publicly available. The analytic methods and study materials used for this analysis will be made available to other researchers for purposes of reproducing the results or replicating the procedure on request.

Risk factors, treatment, and definitions

Information on age, sex, and race were solicited at a screening interview. Participants with a self-reported history of heart disease, stroke, or heart failure were categorized as having a history of CVD. The use of antihypertensive, lipid-lowering, and antidiabetes medication were self-reported. Systolic blood pressure (SBP) was calculated as the mean of three readings obtained following a

standardized protocol. Current smoking was self-reported. Body mass index (BMI) (kg/m^2) was calculated from measured weight (kg) divided by measured height (m) squared. Healthy weight, overweight, and obesity were defined as a BMI ≥ 18.5 to $< 25 \text{ kg}/\text{m}^2$, ≥ 25 to $< 30 \text{ kg}/\text{m}^2$, and $\geq 30 \text{ kg}/\text{m}^2$, respectively. HDL and total cholesterol (TC) (mg/dL) and HbA1C (%) were measured using blood collected during the study visit following standardised procedures. Hypertension was defined as a SBP $\geq 130 \text{ mm Hg}$ or diastolic blood pressure (DBP) $\geq 80 \text{ mm Hg}$ or the use of antihypertensive medication.²² Diabetes was defined as a HbA1C $\geq 6.5\%$ or the use of antidiabetes medication. Dyslipidemia was defined as a total cholesterol $\geq 240 \text{ mg}/\text{dL}$ or the use of lipid-lowering medication. The control of hypertension, diabetes, and dyslipidemia was defined as a SBP/DBP $< 130/80 \text{ mm Hg}$, HbA1C $< 6.5\%$, and TC $< 240 \text{ mg}/\text{dL}$, respectively. The proportion of US adults receiving treatment and controlled risk factor levels were calculated among those with the condition. The proportion with controlled risk factors was also calculated for those treated for the condition. In supplementary analyses, individuals with diabetes were categorised according to HbA1C levels of $< 6.5\%$ (strict control), $\geq 6.5\%$ to $< 7\%$ (intermediate control), $\geq 7\%$ and $< 7.5\%$ (lenient control), and $\geq 7.5\%$ (not controlled). We created a summary score (range 0 to 4) based upon the presence or absence of four risk factors: current smoking, hypertension, diabetes, and dyslipidaemia. Overweight/ obesity was not included as it is causally related to the other risk factors.

Statistical analyses

Age-standardised summary statistics, with 95% confidence intervals (CIs), were computed separately for women and men, using the age distribution for the US adult population in 2015-2016 as the standard. Means were estimated for risk factors measured on a continuous scale and prevalences were estimated for categorical variables. Women-to-men differences, with 95% confidence intervals (CIs), were computed on the absolute scale using linear regression analyses. P-values for sex differences in linear trends across calendar periods were derived by adding an interaction term between sex and calendar period to the model. For each risk factor, participants with missing data

were excluded from the analyses. Subgroup analyses were conducted by age group (20-34, 35-49, 50-64, and 65-79 years), history of CVD, and race (Hispanic, non-Hispanic White, non-Hispanic Black, and Other). Three-way interaction terms were added to the model, which also included the constituent two-way interaction terms, to assess whether sex differences in linear trends differed by age group, history of CVD, and race. To obtain nationally representative values, all analyses were weighted using the NHANES sample weights, thus taking account of the complex sampling design.²³

²⁴ Analyses were performed in R version 3.3.0 using the 'Survey' package.

Results

Data from 35,416 (51% women) participants were analysed (**Supplementary Table 1**). **Table 1** shows the age-standardised risk factor levels and treatment and control rates for women and men in 2013-2016. Results for 2001-2004, 2005-2008 and 2009-2012 are provided in **Supplementary Tables 2, 3, and 4**, respectively.

Blood pressure and hypertension

Changes in SBP over time were similar in women and men: mean levels in 2001-2004 and 2013-2016 were 122 mm Hg and 120 mm Hg, respectively, in women and 124 mm Hg in both calendar periods in men (p for interaction by sex=0.113) (**Figure 1 and Supplementary Table 5**). However, sex differences in SBP trends were present among those aged 50 years or older (p for interaction by sex and age<0.001) (**Figure 2 and Supplementary Table 6** [for 2013-2016 levels]), but did not differ by CVD status or race (**Supplementary Figures 1 and 2**).

Between 2001-2004 and 2013-2016, the prevalence of hypertension decreased from 43% to 42% in women and from 51% to 49% in men (p for interaction by sex=0.085) (**Supplementary Figure 3 and Supplementary Table 5**). Over this calendar period, the percentage of those with hypertension taking antihypertensive medication increased from 52% to 64% in women and from 40% to 53% in men. Similarly, the percentage with controlled blood pressure increased from 16% to

30% in women and from 14% to 22% in men (**Figure 3**). In 2013-2016, sex differences in the prevalence of hypertension were greater in younger than older adults (**Supplementary Table 7**) and treatment and control rates for hypertension were higher among women than men at younger age, but not at older age (**Supplementary Figure 4 and Supplementary Table 8**). Also in 2013-2016, treatment rates were higher among those with than without a history of CVD in both sexes (**Figure 4**) and sex differences in the treatment and control of hypertension were similar across race/ethnic groups (**Supplementary Figure 5**).

Body mass index

Between 2001-2004 and 2013-2016, mean BMI increased from 28.1 kg/m² to 29.6 kg/m² in women and from 27.9 kg/m² to 29.0 kg/m² in men (p for interaction by sex=0.006) (**Figure 1 and Supplementary Table 5**). In 2013-2016, the percentage of women who were overweight was 11 percentage points lower than in men, but women were more often obese (**Table 1**). There were minimal differences in trends across age groups and by CVD status (**Figure 2 and Supplementary Figure 1**). Even though there was no statistical evidence for interaction in trends by race, sex differences in BMI were greatest among Non-Hispanic Black individuals (**Supplementary Figure 2, Supplementary Table 5, and Supplementary Table 6**).

Smoking

Smoking rates decreased from 22% in women and 29% in men in 2001-2004 to 18% in women and 22% in men in 2013-2016 (p for interaction by sex=0.114) (**Figure 1 and Supplementary Table 5**). In both sexes, smoking rates were highest among the youngest adults (**Figure 2 and Supplementary Table 6**). For Hispanics, non-Hispanic blacks, and people of other race-ethnicity, smoking rates were 8 to 10 percentage points lower in women compared with men (**Supplementary Figure 2 and Supplementary Table 6**).

Total and HDL cholesterol and dyslipidemia

Mean HDL cholesterol levels were 58 mg/dL in women and 47 mg/dL in men in 2001-2004 and 60 mg/dL in women and 48 mg/dL in men in 2013-2016 (p for interaction by sex=0.872) (**Figure 1 and Supplementary Table 5**). Reductions in TC were greater in men than women; mean levels were 203 mg/dL in women and 201 mg/dL in men in 2001-2004 and 194 mg/dL in women and 188 mg/dL in men in 2013-2016 (p for interaction by sex= 0.002) (**Figure 1 and Supplementary Table 5**). In each calendar period, TC was similar for women and men aged <35 years, lower among women than men in the 35-49-year range, and then higher in women than men in the two older age groups (**Figure 2**).

The prevalence, treatment, and control of dyslipidemia increased over calendar periods for women and men (**Figure 3**). Compared with women, men were more likely to be treated and to have controlled dyslipidemia, especially at older age (**Supplementary Table 9** [for 2013-2016 rates]). Treatment rates in women vs. men were 40% vs. 48% in 2001-2004 and 56% vs. 67% in 2013-2016. Control rates in women vs. men in the overall population were 33% vs. 40% in 2001-2004 and 50% vs. 63% in 2013-2016. A higher percentage of men than women with CVD had dyslipidemia whereas rates were similar for those without CVD (**Supplementary Table 7** [for 2013-2016 rates]). Sex differences in treatment and control rates differed minimally by CVD status (**Figure 4 and Supplementary Table 9**).

HbA1C and diabetes

Mean levels of HbA1C increased over calendar periods for both women and men (p for interaction by sex=0.835) (**Figure 1 and Supplementary Table 5**). The prevalence of diabetes was lower among women than men (11% vs. 13% in 2013-2016). The prevalence of diabetes increased across calendar periods equally for women and men (p for interaction by sex=0.285) (**Supplementary Figure 3**). Between 2001-2004 and 2013-2016, treatment rates among those with diabetes increased from 76% to 81% in women and from 72% to 80% in men. Control rates were 21% in women and 20% in men in 2001-2004 and 30% vs. 20% in 2013-2016 (p for interaction by sex

=0.159) (**Figure 3 and Supplementary Table 5**). In 2013-2016 there was no evidence of variations in sex differences in treatment and control rates by age, CVD status, and race (**Figure 4, Supplementary Figure 4 and 5, and Supplementary Table 10**). Control rates were similar or higher in women than men in all calendar periods and subgroups, regardless of HbA1C target value (**Supplementary Figure 6 and Supplementary Table 11** [for trends] and **Supplementary Figure 7-9 and Supplementary Table 12-14** [for 2013-2016 rates]).

Number of risk factors

In both sexes, there was no major variation in the distribution of number of risk factors across calendar periods (**Table 1, Supplementary Tables 2-4, and Figure 5**). The percentage of women with no risk factors increased from 36% in 2001-2004 to 40% in 2013-2016. In the same period, the percentage of women with 3 or 4 risk factors increased from 7% to 9%. The percentage of men with no risk factors increased from 26% in 2001-2004 to 31% in 2013-2016 and the percentage with 3 or 4 risk factors increased from 9% in 2001-2004 to 10% in 2013-2016. In both sexes, the percentage with one or more risk factors increased with age and was higher among those with a history of CVD as compared with those with a history of CVD (**Supplementary Figure 10, Supplementary Figure 11, Supplementary Table 15, and Supplementary Table 16** [all for 2013-2016 rates]). Of all race/ethnic groups, Non-Hispanic Black women and men had the highest number of risk factors (**Supplementary Figure 12 and Supplementary Table 17** [both for 2013-2016 rates]).

Discussion

In this study of nationally representative data for US adults between 2001-2004 and 2013-2016, trends in levels, prevalence, treatment, and control of several CVD risk factors were broadly similar between the sexes, but statistically significant sex differences were present in the trends in total cholesterol and BMI levels. Reductions in mean total cholesterol were lesser in women than men, and increases in BMI were greater in women than men. The control of hypertension, diabetes, and

dyslipidemia remains suboptimal in both sexes, whilst a considerable number of women and men continue to smoke. Men were less likely to have control of hypertension and diabetes whereas women were less likely than men to have adequate control of dyslipidemia. Sex differences in treatment rates might in part be responsible for the sex differences in control rates.

The trends in cardiovascular risk factors in the present study are consistent with the sex-specific US estimates from the non-communicable disease risk factor collaboration (NCD-RisC) on global trends in systolic blood pressure, BMI, diabetes, and total cholesterol.^{8, 25-27} While NCD-RisC showed that major geographical variations in risk factor trends exist, sex differences within geographical regions were generally small. Smoking rates differ considerably across the world and the ratio of women-to-men smoking prevalence rates is strongly related to a country's level of economic development.⁷ In the US, and other high-income countries, the women-to-men smoking prevalence ratio is approximately 0.8 but in many low- and middle-income countries this ratio is typically less than 0.1. The present study demonstrates that the women-to-men smoking prevalence ratio in the US differs by race/ethnicity; in 2013-2016 it was 1.0 among non-Hispanic whites, but ranged between 0.48 and 0.66 for the other race-ethnicities. Although the prevalence of smoking has decreased in many countries, only a fifth of countries is on track to reduce the prevalence of smoking by the voluntary global target of 30% in 2025 for men and half are on track for women.²⁸

In agreement with a previous NHANES report,²⁹ the present study indicates that there have been increases in the use of prescription medications to treat hypertension, diabetes, and dyslipidemia in both women and men in the US over the past decades. In 2011-2012, 65% of women and 52% of men had at least one medication prescription, for any indication, and 16% of women and 13% of men used 5 or more medications.²⁹ Antihypertensive and lipid-lowering agents were the most commonly prescribed drugs in both sexes. Despite increases in treatment rates, a substantial proportion of adults are not treated according to current guidelines and many of those treated do not achieve adequate control. Whilst the quality of risk factor management is suboptimal in both sexes, men were less likely to have control of hypertension and diabetes whereas women were less

likely than men to have adequate control of dyslipidemia. As the sex difference in the percentage of individuals with controlled hypertension and dyslipidemia in the overall population was larger than among those treated, our study suggests that sex differences in treatment for hypertension and dyslipidemia underpin some of these differences in control rates.

Inherent sex differences in the biology and pathophysiology of CVD and its underlying mechanisms are likely to explain some of the sex differences present in the current study. Women of younger age tend to have more favourable lipid profiles than men, but cholesterol levels rise after the menopausal transition to levels higher than in men.⁶ The lower rates of hypertension in women than men may be attributable to women's stronger anti-inflammatory immune profile, which may act as a compensatory mechanism to limit increases in blood pressure.⁵ Furthermore, diabetes is a stronger risk factor for CVD in women than men.^{30, 31} It has been suggested that sex differences in body size and body size distribution might contribute to this sex difference,³² as women are diagnosed with diabetes at a higher BMI than men, despite having similar levels of HbA1c.³³ Age-specific CVD rates are lower in women than men, which has often been attributed to a protective effect of sex steroid hormones in women, especially oestrogen. The exact role of sex steroid hormones in explaining women's lower age-specific CVD rates, however, remains uncertain and warrants further investigation. Indeed, oestrogen supplementation does not reduce the risk of CVD in postmenopausal women.³⁴ Also, although CVD rates in women increase with advanced age, there is no major acceleration of rates around the menopause.³⁵ Similarly, sex differences in established risk factors do not fully explain the sex difference in CVD risk.³⁶ For instance, the Tromsø study reported that the higher rate of myocardial infarction among men vs. women persisted throughout life, largely independent of several major risk factors.¹³ Further studies will be needed to assess the impact of sex-specific trends in risk factor levels on sex differences in CVD rates across the lifespan and within different sociodemographic and clinical subpopulations.

The lower rates of CVD in women than men up until the age of 80 years may have contributed to a limited awareness of CVD risk among women themselves and their health care

professionals.^{1, 19, 37} Although awareness of the importance of CVD in women has increased over the past decades,¹⁹ the present study suggests that it has not resulted in major changes in sex differences in the treatment and control of dyslipidemia. Nevertheless, the treatment and control of hypertension continued to be more favourable among women, although their advantage relative to men was smaller in older age. More frequent blood pressure measurements for women of childbearing age might contribute to the early detection and treatment of hypertension among younger women. Moreover, the lower blood pressure levels among women versus men and inherent biological differences may also lead to higher control rates.⁵ Yet, the lower total cholesterol levels among women versus men did not result in higher treatment and control rates of dyslipidemia, suggesting that biological factors alone do not fully explain the sex differences in risk factor control.

Although different treatment guidelines have been in use throughout the study period, differences in recommendations for the use of antihypertensive and lipid-lowering medications could contribute to the opposing patterns in the treatment and control of hypertension and dyslipidemia. The 2013 American College of Cardiology (ACC)/AHA guideline on the treatment of blood cholesterol recommends the use of moderate-to-high-intensity statin therapy for patients with a 10-year risk of atherosclerotic CVD of $\geq 7.5\%$, with LDL cholesterol of 70 to 189 mg/dL and without diabetes or symptomatic CVD.³⁸ The 2017 ACC/AHA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults only recommends antihypertensive medication in the presence of hypertension, with thresholds of ≥ 140 mmHg or DBP ≥ 90 mmHg and 130 to 139 mmHg or DBP 80 to 89 mmHg, depending on CVD risk.²² Due to a higher absolute risk of CVD in men, more men than women with a LDL cholesterol of 70 to 189 mg/dL could be eligible for treatment, whereas there is no scenario where the use of antihypertensive medication is recommended based *exclusively* on 10-year risk of atherosclerotic CVD. Nonetheless, the sex difference in the prevalence of controlled dyslipidemia, in favour of men, was greatest in the older age groups, where most women would also be eligible for treatment based on a 10-year risk of

atherosclerotic CVD of $\geq 7.5\%$. Thus, sex differences in CVD risk alone may not explain the age gradient in the risk factor control. While a better understanding of these age-specific sex differences in the treatment and control of cardiovascular risk factors is required, the present study suggests that a life-course perspective is needed to reduce sex differences in the prevention and management of CVD.

The strengths of the study are the inclusion of a large nationally-representative sample of civilian, noninstitutionalized US women and men. Response rates are high for each calendar period and data are collected using standardised procedures by trained study personnel, including extensive quality control. This study also has some limitations. First, treatment guidelines, diagnostic criteria, and screening practices have changed over time. However, we anticipate that such changes will have affected women and men in a similar way. Furthermore, we defined hypertension, diabetes, and dyslipidaemia consistently over all NHANES surveys, and hence it is unlikely that these changes will have had major effects on our interpretation of sex differences in trends. Second, the NHANES are cross-sectional in design and do not enable direct assessment of the causes of changes in risk factor levels and management and control rates. In addition, we were not able to determine the impact of these sex-specific trends on changes in CVD morbidity and mortality. Third, since each survey includes data from a different sample, sampling error may affect comparisons over time. However, any bias from such issues is likely to be the same for both sexes. Fourth, a substantial number of comparisons were conducted in this study and we cannot exclude the possibility that some of the reported trends were chance findings. In interpreting the findings, the effect size and its clinical implications should therefore be considered alongside the confidence intervals. A further limitation is that some data were self-reported and misreporting could be differential by sex.

In conclusion, trends in SBP, smoking, HDL cholesterol, and HbA1c were broadly similar between the sexes in this nationally representative US sample. Reductions in total cholesterol between 2001-2004 and 2013-2016 were greater in men and BMI increased to a greater extent in women. The control of hypertension, diabetes, and dyslipidemia remains suboptimal in both sexes,

with a lower prevalence of controlled hypertension and diabetes in men and a lower prevalence of controlled dyslipidemia in women. Sex differences in treatment rates might underpin some of the differences in control rates.

Funding

SAEP is supported by a UK Medical Research Council Skills Development Fellowship (MR/P014550/1). MW is supported by an Australian National Health and Medical Research Council fellowship and program grants.

Disclosures

Sanne A.E. Peters: None

Paul Muntner has received grant support from Amgen, Inc.

Mark Woodward has received consulting fees from Amgen, Inc.

References

1. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, Chiuve SE, Cushman M, Delling FN, Deo R, de Ferranti SD, Ferguson JF, Fornage M, Gillespie C, Isasi CR, Jimenez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Lutsey PL, Mackey JS, Matchar DB, Matsushita K, Mussolino ME, Nasir K, O'Flaherty M, Palaniappan LP, Pandey A, Pandey DK, Reeves MJ, Ritchey MD, Rodriguez CJ, Roth GA, Rosamond WD, Sampson UKA, Satou GM, Shah SH, Spartano NL, Tirschwell DL, Tsao CW, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS and Muntner P. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. *Circulation*. 2018;137:e67-e492.
2. Institute for Health Metrics and Evaluation. GBD Compare Data Visualization. 2016.
3. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J and Lisheng L. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet (London, England)*. 2004;364:937-52.
4. Peters SA, Van der Schouw YT, Woodward M and Huxley RR. Sex differences in smoking-related risk of vascular disease and all-cause mortality. *Curr Cardiovasc Risk Rep*. 2015;7:473-79.
5. Gillis EE and Sullivan JC. Sex Differences in Hypertension: Recent Advances. *Hypertension (Dallas, Tex : 1979)*. 2016;68:1322-1327.
6. Wang X, Magkos F and Mittendorfer B. Sex differences in lipid and lipoprotein metabolism: it's not just about sex hormones. *The Journal of clinical endocrinology and metabolism*. 2011;96:885-93.
7. Hitchman SC and Fong GT. Gender empowerment and female-to-male smoking prevalence ratios. *Bulletin of the World Health Organization*. 2011;89:195-202.
8. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. *Lancet (London, England)*. 2016;387:1377-1396.
9. Ali MK, Bullard KM, Saaddine JB, Cowie CC, Imperatore G and Gregg EW. Achievement of goals in U.S. diabetes care, 1999-2010. *The New England journal of medicine*. 2013;368:1613-24.
10. Egan BM, Zhao Y and Axon RN. US trends in prevalence, awareness, treatment, and control of hypertension, 1988-2008. *Jama*. 2010;303:2043-50.
11. Muntner P, Levitan EB, Brown TM, Sharma P, Zhao H, Bittner V, Glasser S, Kilgore M, Yun H, Woolley JM, Farkouh ME and Rosenson RS. Trends in the prevalence, awareness, treatment and control of high low density lipoprotein-cholesterol among United States adults from 1999-2000 through 2009-2010. *The American journal of cardiology*. 2013;112:664-70.
12. Selvin E, Parrinello CM, Sacks DB and Coresh J. Trends in prevalence and control of diabetes in the United States, 1988-1994 and 1999-2010. *Annals of internal medicine*. 2014;160:517-25.
13. Albrektsen G, Heuch I, Lochen ML, Thelle DS, Wilsgaard T, Njolstad I and Bonaa KH. Lifelong Gender Gap in Risk of Incident Myocardial Infarction: The Tromso Study. *JAMA internal medicine*. 2016;176:1673-1679.
14. Leening MJ, Ferket BS, Steyerberg EW, Kavousi M, Deckers JW, Nieboer D, Heeringa J, Portegies ML, Hofman A, Ikram MA, Hunink MG, Franco OH, Stricker BH, Witteman JC and Roos-Hesselink JW. Sex differences in lifetime risk and first manifestation of cardiovascular disease: prospective population based cohort study. *BMJ (Clinical research ed)*. 2014;349:g5992.
15. American Heart Association. Go Red For Women. 2017. Available at: <https://www.goredforwomen.org/>. Accessed April 3, 2018.
16. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, Newby LK, Pina IL, Roger VL, Shaw LJ, Zhao D, Beckie TM, Bushnell C, D'Armiento J, Kris-Etherton PM, Fang J, Ganiats TG, Gomes AS, Gracia CR, Haan CK, Jackson EA, Judelson DR, Kelepouris E, Lavie CJ, Moore A, Nussmeier NA, Ofili E, Oparil S, Ouyang P, Pinn VW, Sherif K, Smith SC, Jr., Sopko G, Chandra-Strobo N, Urbina EM, Vaccarino V and Wenger NK. Effectiveness-based guidelines for the prevention of

cardiovascular disease in women--2011 update: a guideline from the american heart association. *Circulation*. 2011;123:1243-62.

17. Mosca L, Appel LJ, Benjamin EJ, Berra K, Chandra-Strobos N, Fabunmi RP, Grady D, Haan CK, Hayes SN, Judelson DR, Keenan NL, McBride P, Oparil S, Ouyang P, Oz MC, Mendelsohn ME, Pasternak RC, Pinn VW, Robertson RM, Schenck-Gustafsson K, Sila CA, Smith SC, Jr., Sopko G, Taylor AL, Walsh BW, Wenger NK and Williams CL. Evidence-based guidelines for cardiovascular disease prevention in women. *Circulation*. 2004;109:672-93.

18. Mosca L, Banka CL, Benjamin EJ, Berra K, Bushnell C, Dolor RJ, Ganiats TG, Gomes AS, Gornik HL, Gracia C, Gulati M, Haan CK, Judelson DR, Keenan N, Kelepouris E, Michos ED, Newby LK, Oparil S, Ouyang P, Oz MC, Petitti D, Pinn VW, Redberg RF, Scott R, Sherif K, Smith SC, Jr., Sopko G, Steinhorn RH, Stone NJ, Taubert KA, Todd BA, Urbina E and Wenger NK. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. *Circulation*. 2007;115:1481-501.

19. Mosca L, Mochari-Greenberger H, Dolor RJ, Newby LK and Robb KJ. Twelve-year follow-up of American women's awareness of cardiovascular disease risk and barriers to heart health. *Circulation Cardiovascular quality and outcomes*. 2010;3:120-7.

20. National Center for Health Statistics. Specifying Weighting Parameters. Available at: <https://www.cdc.gov/nchs/tutorials/nhanes/surveydesign/weighting/intro.htm>. Accessed April 14 2018.

21. National Center for Health Statistics. National Health and Nutrition Examination Survey. Available at: <https://www.cdc.gov/nchs/nhanes/index.htm>. Accessed April 5 2018.

22. Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC, Jr., Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA, Sr., Williamson JD and Wright JT, Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension (Dallas, Tex : 1979)*. 2018;71:e13-e115.

23. Chen T, Parker J, Clark J, Shin H, Rammon J and Burt V. National Health and Nutrition Examination Survey: Estimation procedures, 2011–2014. National Center for Health Statistics. *Vital Health Stat* 2(177). 2018.

24. National Center for Health Statistics. National Health and Nutrition Examination Survey: Survey Methods and Analytic Guidelines. Available at <https://www.cdc.gov/nchs/nhanes/analyticguidelines.aspx>. Accessed July 5 2018

25. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet (London, England)*. 2016;387:1513-30.

26. Farzadfar F, Finucane MM, Danaei G, Pelizzari PM, Cowan MJ, Paciorek CJ, Singh GM, Lin JK, Stevens GA, Riley LM and Ezzati M. National, regional, and global trends in serum total cholesterol since 1980: systematic analysis of health examination surveys and epidemiological studies with 321 country-years and 3.0 million participants. *Lancet (London, England)*. 2011;377:578-86.

27. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet (London, England)*. 2017;389:37-55.

28. Bilano V, Gilmour S, Moffiet T, d'Espaignet ET, Stevens GA, Commar A, Tuyl F, Hudson I and Shibuya K. Global trends and projections for tobacco use, 1990-2025: an analysis of smoking indicators from the WHO Comprehensive Information Systems for Tobacco Control. *Lancet (London, England)*. 2015;385:966-76.

29. Kantor ED, Rehm CD, Haas JS, Chan AT and Giovannucci EL. Trends in Prescription Drug Use Among Adults in the United States From 1999-2012. *Jama*. 2015;314:1818-31.

30. Peters SA, Huxley RR and Woodward M. Diabetes as risk factor for incident coronary heart disease in women compared with men: a systematic review and meta-analysis of 64 cohorts including 858,507 individuals and 28,203 coronary events. *Diabetologia*. 2014;57:1542-51.
31. Peters SA, Huxley RR and Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775,385 individuals and 12,539 strokes. *Lancet (London, England)*. 2014;383:1973-80.
32. Peters SAE and Woodward M. Sex Differences in the Burden and Complications of Diabetes. *Current diabetes reports*. 2018;18:33.
33. Logue J, Walker JJ, Colhoun HM, Leese GP, Lindsay RS, McKnight JA, Morris AD, Pearson DW, Petrie JR, Philip S, Wild SH and Sattar N. Do men develop type 2 diabetes at lower body mass indices than women? *Diabetologia*. 2011;54:3003-6.
34. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM and Ockene J. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *Jama*. 2002;288:321-33.
35. Bots SH, Peters SAE and Woodward M. Sex differences in coronary heart disease and stroke mortality: a global assessment of the effect of ageing between 1980 and 2010. *BMJ global health*. 2017;2:e000298.
36. Huxley R, Woodward M, Barzi F, Wong JW, Pan WH and Patel A. Does sex matter in the associations between classic risk factors and fatal coronary heart disease in populations from the Asia-Pacific region? *Journal of women's health (2002)*. 2005;14:820-8.
37. Mosca L, Linfante AH, Benjamin EJ, Berra K, Hayes SN, Walsh BW, Fabunmi RP, Kwan J, Mills T and Simpson SL. National study of physician awareness and adherence to cardiovascular disease prevention guidelines. *Circulation*. 2005;111:499-510.
38. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC, Jr., Watson K, Wilson PW, Eddleman KM, Jarrett NM, LaBresh K, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC, Jr. and Tomaselli GF. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:S1-45.

Figure legend

Figure 1 Trends in systolic blood pressure, body mass index, current smoking, total cholesterol, HDL cholesterol, and HbA1c, by sex

Solid lines are for men and dashed lines are for women. All estimates are age-standardized to the US standard population in 2015-2016. Error bars indicate 95% confidence intervals.

Figure 2 Trends in systolic blood pressure, body mass index, current smoking, total cholesterol, HDL cholesterol, and HbA1c, by sex and age group

Solid lines are for men and dashed lines are for women. All estimates are age-standardized to the US standard population in 2015-2016. Error bars indicate 95% confidence intervals.

Figure 3 Treatment and control of hypertension, diabetes, and dyslipidemia, by sex and calendar period

Black areas represent treated and controlled cases. Grey areas represent treated but uncontrolled cases. Light grey areas represent untreated and uncontrolled cases. Hypertension was defined as a systolic/diastolic blood pressure $\geq 130/80$ mmHg or the use of antihypertensive medication. Diabetes was defined as a HbA1C $\geq 6.5\%$ or the use of antidiabetes medication. Dyslipidemia was defined as a total cholesterol ≥ 240 mg/dL or the use of lipid-lowering medication. The control of hypertension, diabetes, and dyslipidemia, respectively, were defined as a systolic/diastolic blood pressure $< 130/80$ mmHg, HbA1C $< 6.5\%$, and total cholesterol < 240 mg/dL.

Figure 4 Treatment and control of hypertension, diabetes, and dyslipidemia in 2013-2016, by sex and history of CVD

Black areas represent treated and controlled cases. Grey areas represent treated but uncontrolled cases. Light grey areas represent untreated and uncontrolled cases. Hypertension was defined as a systolic/diastolic blood pressure $\geq 130/80$ mmHg or the use of antihypertensive medication. Diabetes was defined as a HbA1C $\geq 6.5\%$ or the use of antidiabetes medication. Dyslipidemia was defined as a total cholesterol ≥ 240 mg/dL or the use of lipid-lowering medication. The control of hypertension, diabetes, and dyslipidemia, respectively, were defined as a systolic/diastolic blood pressure $< 130/80$ mmHg, HbA1C $< 6.5\%$, and total cholesterol < 240 mg/dL.

Figure 5 Trends in the number of risk factors, by sex and age group

Risk factors were current smoking, hypertension, dyslipidemia, and diabetes. Black areas represent individuals without risk factors. Dark grey areas represent individuals with one risk factor. Grey areas represent individuals with two risk factors. Light grey areas represent individuals with three or four risk factors.

Table 1: Age-standardized prevalence of risk factors, treatment, and control in 2013-2016, by sex

	Women	Men	Women vs. men
Age, years	47.2 (16.1)	47.5 (16.3)	-
Race, %			
Hispanic	28.8	26.4	-
Non-Hispanic white	35.8	37.4	-
Non-Hispanic black	20.7	20.7	-
Other	14.7	15.6	-
Risk factors			
Systolic BP, mmHg	119.8 (119.3, 120.3)	124.1 (123.4, 124.8)	-4.3 (-5.0, -3.5)
Current smoking, %	18.4 (16.6, 20.3)	21.7 (19.8, 23.6)	-3.3 (-5.0, -1.5)
BMI, kg/m ²	29.6 (29.3, 30.0)	29.0 (28.7, 29.3)	0.6 (0.3, 0.9)
Healthy weight, %	29.9 (28.2, 31.6)	24.2 (22.5, 26.0)	5.7 (3.5, 7.9)
Overweight, %	26.9 (25.6, 28.2)	37.8 (35.7, 39.8)	-10.9 (-13.6, -8.2)
Obese, %	41.6 (39.8, 43.4)	36.8 (34.4, 39.2)	4.8 (2.1, 7.5)
Total cholesterol, mg/dL	193.9 (192.4, 195.4)	188.3 (186.3, 190.4)	5.5 (3.5, 7.5)
HDL cholesterol, mg/dL	59.8 (58.9, 60.6)	48.2 (47.5, 48.9)	11.6 (10.8, 12.3)
HbA1C, %	5.6 (5.6, 5.6)	5.7 (5.6, 5.7)	-0.1 (-0.1, 0.0)
History of CVD, %	5.8 (4.9, 6.7)	8.1 (7.0, 9.1)	-2.3 (-3.7, -0.8)
Treatment and control			
Hypertension, %	42.1 (40.8, 43.5)	49.1 (46.8, 51.5)	-7.0 (-9.6, -4.4)
Treated, %	64.1 (61.3, 66.9)	53.6 (51.1, 56.1)	10.5 (7.5, 13.5)
Controlled among treated, %	46.8 (43.1, 50.5)	41.3 (37.3, 45.3)	5.6 (0.8, 10.3)
Controlled among overall population, %	30.0 (26.8, 33.2)	22.1 (19.4, 24.9)	7.9 (4.5, 11.3)
Diabetes, %	10.8 (9.7, 11.8)	13.0 (11.7, 14.2)	-2.2 (-3.6, -0.7)
Treated, %	80.8 (77.8, 83.9)	80.2 (75.6, 84.8)	0.6 (-3.9, 5.2)
Controlled among treated, %	36.5 (30.5, 42.4)	24.7 (19.2, 30.2)	11.8 (4.3, 19.2)
Controlled among overall population, %	29.5 (24.5, 34.5)	19.8 (14.9, 24.7)	9.7 (3.5, 15.8)
Dyslipidemia, %	25.9 (24.2, 27.5)	29.5 (28.0, 31.1)	-3.7 (-5.9, -1.4)
Treated, %	56.1 (52.3, 59.8)	67.5 (64.0, 71.0)	-11.5 (-15.5, -7.5)
Controlled among treated, %	90.1 (87.4, 92.7)	93.7 (91.8, 95.7)	-3.7 (-6.5, -0.8)
Controlled among overall population, %	50.5 (46.6, 54.3)	63.3 (60.0, 66.6)	-12.8 (-17.2, -8.5)
Number of risk factors*			
None	40.0 (38.3, 41.6)	31.0 (28.5, 33.5)	9.0 (6.7, 11.2)
1 risk factor	31.5 (29.9, 33.0)	34.9 (32.8, 36.9)	-3.4 (-5.7, -1.1)
2 risk factors	19.5 (18.6, 20.4)	23.8 (22.3, 25.2)	-4.2 (-5.7, -2.7)
3 or 4 risk factors	9.0 (8.0, 10.1)	10.4 (9.1, 11.7)	-1.4 (-3.1, 0.3)

Age and race are sample means (standard deviation) and percentages, respectively. Other values are means for continuous variables and percentages for categorical variables, age-standardized to the US standard population in 2015-16. Values between brackets indicate 95% confidence intervals.

* Risk factors were current smoking, hypertension, dyslipidemia, and diabetes. Participants with a self-reported Asian background were included in the 'other' group. BP; blood pressure; BMI, body mass index; HDL; high-density lipoprotein; CVD, cardiovascular disease