

Cardiovascular Disease: The Basics

Cardiovascular disease (CVD) is the leading cause of death for both men and women worldwide.¹

The WHO explains that CVD represents a group of heart and blood vessel disorders including the following:²

- Coronary heart disease (CHD): a disease of the blood vessels supplying the heart muscle;
- Cerebrovascular disease: a disease of the blood vessels supplying the brain;
- Peripheral arterial disease: a disease of blood vessels supplying the arms and legs;
- Rheumatic heart disease: damage to the heart muscle and heart valves from rheumatic fever, caused by streptococcal bacteria;
- Congenital heart disease: malformations of heart structure existing at birth; and
- Deep vein thrombosis and pulmonary embolism: blood clots in the leg veins, which can dislodge and move to the heart and lungs.

This group of diseases was estimated to be responsible for 31% of all global deaths in 2015 which represents approximately 17.7 million people.³ 80% of these deaths are due to heart attacks and strokes,⁴ acute events that are mainly caused by a blockage which prevents blood from flowing to the heart or the brain.⁵ Both of these events can be life-threatening and require immediate emergency treatment and hospitalisation.

Roughly three-quarters of all CVD-related deaths took place in low- and middle-income countries,⁶ and while it is still the leading cause of death across high-income countries, CVD also represents a major cause of serious illness and disability in these countries. It is both a threat to sufferers' quality of life as well as a significant burden for healthcare systems. The CDC estimates that \$1 out of every \$6 spent on healthcare in the United States is spent on treatment of CVD.⁷ Eurostat estimates that the disease represents an average annual spend in the European Union of €372 per inhabitant, or a total of €169 billion.⁸

Risk factors for CVD

There are various risk factors that studies have found are associated with developing CVD, including the following:^{9,10,11,12,13}

- Physical inactivity
- Unhealthy diet
- High blood pressure
- High cholesterol
- Being obese or overweight
- Use of combustible tobacco products
- Excessive alcohol consumption
- Diabetes
- Family history of CVD
- Age (and, for women, menopause)
- Sex (men are more likely to develop CVD at a younger age)
- Stress
- Race/ethnicity (in the US, American Indians or Alaska Natives are less likely to die from CVD,¹⁴ while in the UK CVD is more common in people with a South Asian and African or Caribbean background¹⁵)
- Prior history of pre-eclampsia during pregnancy¹⁶

CVD, sex/gender and age

The risk of CVD in women is still underestimated by society, including women themselves, and the medical community. CVD has usually been thought of as a male disease and it is only during the last few decades that there is increasing awareness about how CVD affects women differently.¹⁷ In the European Union the disease is the leading cause of death for women. In 2013, the most recent year for which Eurostat has this data available, CVD accounted for 37.5% of all deaths in the EU. However, these figures are different for men and women. 34.4% of men who died that year did so as a result of CVD, but that figure rises to 40.5% for women.¹⁸

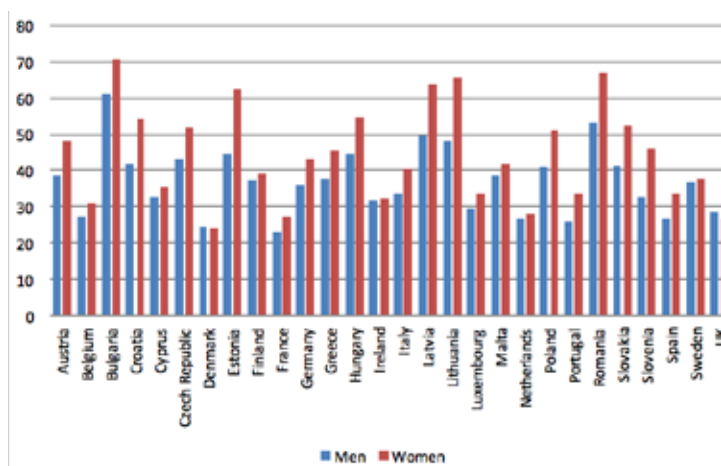


Figure 1. Percentage of total deaths due to CVD in EU Member States by gender, 2013.

Figure 1. below presents the percentage of total deaths of men and women due to CVD. We can see that for only two countries is the share of deaths due to CVD greater for men than for women (Denmark and the United Kingdom). We can also see that the gender gap varies substantially; it is narrowest in Ireland (at only 0.2) but rises to 17.6 in Estonia.

As the sections below outline, CVD represents a particular challenge to women's health which must be addressed as such by policymakers and healthcare professionals.

Risk factors and sex/gender

Women's experience of CVD is different from men's. Women are much more likely to die within a year of having had a heart attack than men.¹⁹ Rates of CVD have peaked and are declining in advanced industrialised countries, even as they rise in developing nations.²⁰ This decline has been smaller for women and, coupled with their greater longevity, this means that the burden of CVD is gradually shifting onto women.²¹ Gender differences in the risk factors for developing CVD can help to explain differences in women's experience of the disease.

Lifestyle factors, such as tobacco smoking, lack of daily fruit and vegetable consumption, and physical inactivity are important predictors of CVD.²² They represent modifiable risk factors that are amenable to intervention in order to reduce the risk of developing non-communicable diseases like CVD.

Women are less likely to be physically active than men,²³ and though women tend to smoke less than men²⁴ smoking appears to have a particularly harmful effect on women.²⁵ While smoking increases the risk of CVD for men and women,^{26,27,28,29} it is estimated that women who smoke between three and five cigarettes double their risk of heart attack; men would need to smoke between six and nine cigarettes to experience a similar increase in their risk of experiencing a heart attack.³⁰ For women who smoke and use oral contraceptives, the risk of stroke, heart attack, blood clots, and peripheral vascular disease is further increased.^{31,32} More research is needed to understand why women who smoke have an increased risk of CVD as the underlying mechanism remains unclear.

Women are protected by their hormones against CVD during their fertile years, but lose this protection once they enter menopause.^{33,34,35,36,37} The onset of CVD therefore tends to be later in women than it is in men.^{38,39} However, after menopause a reduction in hormone levels is interlinked with a web of other risk factors such as obesity, diabetes, hyperlipidaemia, hypertension, history of smoking, and metabolic syndrome.⁴⁰

Hypertension increases in women over the age of 45, as does total cholesterol level.⁴¹ Obesity, another major CVD risk factor, is more prevalent in men under the age of 45 than in women.⁴² However, the risk of developing obesity however increases with advancing years in women.⁴³

In addition, the risk of developing CVD for those with diabetes is greater for women than it is for men.^{44,45,46} One meta-analysis of 37 studies finds that the risk of death from coronary heart disease is 50% higher in women with diabetes than it is in men with diabetes.⁴⁷ It is important to note also that gestational diabetes (a form of diabetes that occurs during pregnancy)⁴⁸ increases the risk of developing types 2 diabetes later in life.⁴⁹ As much as half of all women who experienced gestational diabetes during their pregnancy will develop type 2 diabetes within 5 years of the birth,⁵⁰ further impacting on the likelihood of subsequently developing CVD.

Thus, it is clear that women have a different experience of CVD than men. While younger women have a lower prevalence of CVD compared to men, this gap narrows and even reverses in older women.⁵¹

CVD symptoms and gender

Common symptoms of CVD include the following:^{52,53}

- Chest pain, tightness, or discomfort
- Shortness of breath
- Pain, numbness, weakness, or cold in the limbs
- Dizziness, light-headedness, or fainting
- Slow, racing, or irregular heartbeat
- Weakness or fatigue
- Swollen feet or ankles
- Difficulty seeing with one or both eyes
- Numbness of the face, arm, or leg (particularly on one side of the body)
- Confusion, difficulty speaking or understanding speech

However, in women the symptoms of CVD can be different from these commonly observed ones and this, in addition to the prevalent belief that CVD is a male disease, may add to the under-recognition of CVD in women.^{54,55}

For example, while women may experience chest pain while having a heart attack, this pain may be less pronounced than in men. Instead there may be an uncomfortable pressure in the centre of the chest which can last a few minutes, or come and go. In addition, they may experience pain or discomfort in one or both arms, the back, neck, jaw or stomach, shortness of breath with or without chest discomfort, or breaking out in a cold sweat, nausea/vomiting, light-headedness or a general feeling of weakness.

Doctors sometimes mistake symptoms of CVD in women for stress, panic disorder, or even hypochondria.⁵⁶ Women are also often slower to react when such symptoms strike, often losing valuable time in seeking emergency treatment.^{57,58} Even after an acute coronary event has been experienced, women in Europe experience worse outcomes than men with respect to targets for metrics such as blood pressure and cholesterol.⁵⁹ It is crucial therefore that women and their doctors be educated as to what symptoms of CVD can look like in women, and that caregivers take sex and gender into account when formulating treatment plans.

CVD, gender and depression

Psychosocial factors are important in the prevention and treatment of CVD.⁶⁰ For individuals with depression, outcomes for people after a CVD event are more unfavourable.⁶¹ Unfortunately, cardiologists are usually not trained in recognising mental health problems which can be responsible for women failing to adopt a healthier lifestyle and which would prevent another heart attack.⁶²

There is growing evidence that the prevalence of depression and various forms of sustained mental stress (anxiety, anger, marital conflicts, work stress etc.) is substantially higher in female patients after acute myocardial infarction (AMI) compared to men, particularly in younger age groups.⁶³ While it is important to note that few women develop CVD as young adults,⁶⁴ this link between depression and CVD should raise concern since a younger age has been identified as a particularly vulnerable phase in which depression significantly acts on premature CVD. There is increasing evidence that patients, who succeed in a substantial reduction of their depression symptoms have a better CVD prognosis than those who did not.

In the complex field of chronic diseases, treating each disease in isolation would seem to be one of the biggest challenges to overcome. Rethinking of policy, medical training, and treatment will be required to better address the chronic disease burden for both women and men.

Pregnancy and CVD

Pregnancy can be thought of as a stress-test for heart disease in women. Hypertensive disorders affect approximately 5-10% of all pregnancies and are important contributors to maternal and neonatal morbidity and mortality worldwide.^{65,66} In high income countries, mortality rates among pregnant women are generally low, but heart disease has been identified as the leading cause of death during pregnancy.⁶⁷ The severe forms of hypertensive pregnancy disorders, preeclampsia and the HELLP-syndrome, lead to a two-fold increase in future CVD risk and are now acknowledged as a CVD risk factor.^{68,69}

To address the lack of understanding and guidance of heart disease in pregnancy, the European Society of Cardiology set up the first formal CVD pregnancy registry in 2007. Reassuringly, results from the pregnancy registry show that most women with heart disease can go through pregnancy and delivery safely, as long as they are adequately evaluated, receive counselling, and high-quality care.

However, to confound matters, many symptoms of heart disease – such as shortness of breath, fatigue, and heartburn – are similar to general pregnancy symptoms, making heart disease during pregnancy difficult to recognise and diagnose. Women suffering from a congenital heart disease need to be careful with regard to pregnancy and birth control options as both can increase heart risk in vulnerable populations.⁷⁰

Hormone Replacement Therapy (HRT) and CV

Hormone Replacement Therapy (HRT) is a drug treatment that is used to replace female sex hormones in women when production slows and ceases as a result of the menopause.⁷¹ The impact of HRT on cardiovascular diseases has been a concern for women and their doctors for some time. In the 1980s and 1990s, HRT was routinely prescribed to women in order to relieve menopausal symptoms, but also because it was believed that the therapy would reduce the risk of heart disease.⁷² This effect was expected due to the role that female sex hormones play in keeping young women's hearts healthy, which explains why CVD tends to emerge in post-menopausal women.⁷³

However, the results of HRT in this respect have been mixed.⁷⁴ While some randomised controlled trials did indicate that HRT therapy led to a decrease in cardiovascular events,⁷⁵ or at the very least failed to elevate cardiovascular risks,^{76,77} currently the consensus is that in general postmenopausal women do not benefit from HRT.⁷⁸ By 2004 the American Heart Association's *Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women* acknowledged that HRT did not constitute a preventative treatment for CVD.⁷⁹ Use of HRT has consequently declined.

Some recent research suggests that the beneficial effects of certain types of HRT medication may not materialise until several years after the treatment has first begun but there is no evidence to support a general recommendation for the treatment of menopausal and older women⁸⁰ and the AHA's guidelines around the treatment remain unchanged.

More research is required to understand "influences of timing, duration, dose, route of administration, and agents on menopausal hormone treatment-related risks and benefits".⁸¹

Under-representation of women in clinical trials

Historically women have been under-represented in CVD clinical trials due to the mistaken belief that this disease mostly affects men. General clinical trial practice that is one size-fits-all and fails to stratify trials according to sex and age must be revised in order to include a robust risk/benefit analysis for both sexes.

Women with CVD have had to face the double discrimination of sex and age. Cost may have been another consideration, as women's hormonal fluctuations tend to complicate the pharmacokinetic and pharmacodynamic picture. Paradoxically, CVD in women appears to be greatly influenced by hormones, a factor that has been used to exclude them from clinical studies.

Moreover, if women have been included in clinical trials, results were not powered nor rigorously analysed for gender differences. Unless such a systematic analysis is made a legal requirement, the future looks bleak for women. CVD, the leading cause of death for women, is a glaring example of the lack of evidence how medicines work in women. Even in the US, where it is a legal requirement that research funded by the taxpayer's money must include women and minority groups in the research, this is not standard practice. A recent study found that trials by the National Heart Lung and Blood Institute, attached to the National Institutes of Health (NIH), included as little as 38% women for the years 1965 and 1998 and 27% between 1997 and 2006.⁸² Furthermore, only 13 of 19 studies analysed the sex/gender differences.

Gender-based CVD research fares even worse in Europe.⁸³ The European regulator, the European Medicines Agency, responsible for approving medicines in Europe, must make gender and age analysis a legal requirement for approval to ensure that women and older people get evidence-based medicines.

European and national strategies for CVD prevention

It is estimated that approximately 80% of all instances of CVD could be eliminated if people were to adopt necessary lifestyle modifications.⁸⁴ Being obese or overweight, being physically inactive, having diabetes, and smoking are some important predictors of CVD.

Existing policy at European-level aims to address these risk factors directly. For example, the WHO's *Action Plan for implementation of the European Strategy for the Prevention and Control of Noncommunicable Diseases 2012–2016* focused on making diets healthier and increasing physical activity.⁸⁵ In addition, the European Union and its Member States take the issue of smoking seriously.⁸⁶ The contents, packaging, and labelling of tobacco products is regulated at EU-level and the Tobacco Advertising Directive (2003/33/EC) places strict limits on advertising or sponsorship which promotes a tobacco product. The EU has also run several anti-tobacco campaigns targeting different age groups (the HELP campaign targeted young people aged 15 to 25, while Ex-Smokers are Unstoppable focused on 25 to 34 year olds).⁸⁷

There have also been a number of actions taken at EU-level that directly address the issue of CVD. In 2004 the European Council produced *Council Conclusions on Promoting Heart Health* which called upon the Commission as well as individual Member States to take action to address CVD.⁸⁸ 2005's Luxembourg declaration produced by the Commission represented an agreement between representatives of National Ministries of Health, as well as cardiac and heart foundations at both European and National levels. These bodies agreed to initiate or strengthen comprehensive CVD prevention plans, as well as to produce a consensus document highlighting the core principles of CVD prevention.

This document was the *European Heart Health Charter*, launched in 2007. It was developed by the European Heart Network, an organisation of European heart foundations and NGOs,⁸⁹ the European Society of Cardiology in conjunction with the European Commission and the World Health Organisation (WHO) Regional Office for Europe. This charter aims to prevent cardiovascular disease in Europe.⁹⁰ It advocates for the education of the public, the empowerment of patients, and in particular the targeting of risk factors related to lifestyle.⁹¹ It also aims to mobilise broad support to promote cardiovascular health and to prevent CVD.

Finally, the European Commission has funded research on different aspects of CVD, including it as one of five areas of 'Translational research in other major diseases' in the Commission's Seventh Framework Programme (FP7 2007-2013).⁹² FP7's first five years saw an EU contribution of approximately €163 million on collaborative disease research projects as part of the HEALTH programme.

Steps for Policy Action

1. Improve existing EU data collection on CVD.

Currently CVD data collection at the EU remains limited. Annual data about incidence and prevalence should also include the interaction and influence of major risk factors, presence of other chronic diseases, disaggregated by gender and age in order to fully understand CVD trends.

2. Examine the interaction between CVD, gender, age, and other chronic diseases in women.

Large gender differences exist in the development and progression of CVD in women. As women live longer and the prevalence of chronic diseases such as diabetes increases, it is important to understand the role that gender, age, and the interaction with other chronic conditions contribute to the development of CVD to better prevent and manage the overall chronic disease burden in women.

3. Include women in clinical trials to develop evidence-based prevention, medicines, diagnostic and medical devices for women.

Women, especially older women who are at particular risk of CVD, need to be included in statistically relevant numbers in clinical trials to ensure the approved medicine and treatments work effectively in women.

4. Make smoking cessation policy and programmes gender sensitive in order to effectively reach young girls and women to stop smoking, thereby eliminating a major risk for CVD in women.

Rates of smoking among young women are on the rise across Europe, with grave consequences for their future health and well-being. Studies demonstrate the alarming impact that smoking has on women and CVD. Tobacco-control programmes should target women, particularly disadvantaged groups, and women in those countries where smoking among young women is increasing.

5. Tackle Europe's obesity crisis, by making women as family caregivers more health-literate about the role of diet and exercise in preventing CVD and other chronic diseases.

The risk of CVD can be lowered through healthy lifestyle choices. An unhealthy diet, lack of exercise and obesity are strongly linked to CVD.

6. Increase awareness of CVD risk among women, particularly among older women.

CVD remains the top killer of women in Europe and is responsible for much illness. Increased awareness of risk factors and symptoms is needed in order to combat this major cause of morbidity, mortality and disability in later years.

7. Improve training of medical professionals in how to prevent and treat CVD in women and establish prevention and treatment guidelines.

Major medical societies need to ensure that the acquired knowledge is widely distributed in the form of prevention and treatment guidelines that are rigorously implemented and followed. General practitioners need to better understand the complexity of CVD and the interconnection with lifestyle factors and other chronic diseases, trained to recognise symptoms, improve diagnosis and treat their patients according to the latest scientific sex and gender knowledge and standards of care.

8. Policy makers, researchers, clinicians, regulators must engage in a concerted effort to reduce the burden of chronic diseases by taking a gender-sensitive and multi- and interdisciplinary approach reaching across the lifespan of women and men.

The Joint Action for Chronic diseases is an opportunity to consider sex and age factors in a comprehensive approach to tackle Europe's chronic disease burden. Consideration of women and older patients must be included in this initiative.

A warm thank you to our expert reviewer:

Marco Stramba-Badiale, MD: PhD Director, Department of Geriatrics and Cardiovascular Medicine IRCCS Istituto Auxologico Italiano, Milan Italy

Contributors: Hildrun Sundseth, Peggy Maguire, Kristin Semancik and Lisa Keenan
December 2017

European Institute of Women's Health, CLG

33 Pearse Street, Dublin 2, Ireland

Telephone: +353-1-671 5691

Email: info@eurohealth.ie

Website: www.eurohealth.ie

Registered Charity #20035167

References

- WHO. 2016. *Global Health Estimates 2015: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2015*. http://www.who.int/healthinfo/global_burden_disease/estimates/en/
- WHO. 2017. *Cardiovascular diseases (CVDs): Fact Sheet*. <http://www.who.int/mediacentre/factsheets/fs317/en/>
- WHO. 2017. *Cardiovascular diseases (CVDs): Fact Sheet*. <http://www.who.int/mediacentre/factsheets/fs317/en/>
- WHO. 2017. *Cardiovascular disease*. http://www.who.int/cardiovascular_diseases/en/
- WHO. 2017. *Cardiovascular diseases (CVDs): Fact Sheet*. <http://www.who.int/mediacentre/factsheets/fs317/en/>
- WHO. 2017. *Cardiovascular disease*. http://www.who.int/cardiovascular_diseases/en/
- CDC. 2016. *At a Glance 2016: Heart Disease and Stroke*. <https://www.cdc.gov/chronicdisease/resources/publications/aag/pdf/2016/aag-heart-disease.pdf>
- Eurostat. 2016. *Cardiovascular Disease Statistics*. http://ec.europa.eu/eurostat/statistics-explained/index.php/Cardiovascular_diseases_statistics
- WHO. 2017. *Cardiovascular diseases (CVDs): Fact Sheet*. <http://www.who.int/mediacentre/factsheets/fs317/en/>
- CDC. 2016. *At a Glance 2016: Heart Disease and Stroke*. <https://www.cdc.gov/chronicdisease/resources/publications/aag/pdf/2016/aag-heart-disease.pdf>
- NHS. 2016. *Cardiovascular Disease*. <https://www.nhs.uk/conditions/cardiovascular-disease/>
- HSE. 2017. *Cardiovascular Disease*. <http://www.hse.ie/eng/health/az/C/Cardiovascular-disease/>
- British Heart Foundation. 2017. *Cardiovascular Disease*. <https://www.bhf.org.uk/heart-health/conditions/cardiovascular-disease>
- CDC. 2017. *Heart Disease Facts*. <https://www.cdc.gov/heartdisease/facts.htm>
- NHS. 2016. *Cardiovascular Disease*. <https://www.nhs.uk/conditions/cardiovascular-disease/>
- Bellamy, L., Casas, J.P., Hingorani, A.D. and Williams, D.J., 2007. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *Bmj*, 335(7627), p.974.
- Maas, Angela HEM, Yvonne T. van der Schouw, Vera Regitz-Zagrosek, Eva Swahn, Yolande E. Appelman, Gerard Pasterkamp, Hugo Ten Cate et al. "Red alert for women's heart: the urgent need for more research and knowledge on cardiovascular disease in women: proceedings of the workshop held in Brussels on gender differences in cardiovascular disease, 29 September 2010." *European Heart Journal* 32, no. 11 (2011): 1362-1368.
- Eurostat. 2013. *Cardiovascular diseases statistics*. http://ec.europa.eu/eurostat/statistics-explained/index.php/Cardiovascular_diseases_statistics
- Harvard Health Publishing. 2017. *Gender matters: Heart disease risk in women*. <https://www.health.harvard.edu/heart-health/gender-matters-heart-disease-risk-in-women>
- Luepker, Russell V. "Cardiovascular disease: rise, fall, and future prospects." *Annual review of public health* 32 (2011): 1-3.
- Towfighi, Amytis, Ling Zheng, and Bruce Ovbiagele. "Sex-specific trends in midlife coronary heart disease risk and prevalence." *Archives of internal medicine* 169, no. 19 (2009): 1762-1766.
- Buttar, Harpal S., Timao Li, and Nivedita Ravi. "Prevention of cardiovascular diseases: Role of exercise, dietary interventions, obesity and smoking cessation." *Experimental & Clinical Cardiology* 10, no. 4 (2005): 229.
- European Heart Network. 2017. *European Cardiovascular Disease Statistics 2017*. <http://www.ehnheart.org/cvd-statistics.html>
- WHO. 2015. *Global Health Observatory (GHO) data: Tobacco use*. <http://apps.who.int/gho/data/view.main.1805WB?lang=en>
- Prescott, Eva, Merete Hippe, Peter Schnorh, Hans Ole Hein, and Jørgen Vestbo. "Smoking and risk of myocardial infarction in women and men: longitudinal population study." *Bmj* 316, no. 7137 (1998): 1043-1047.
- WHO. 2017. *Cardiovascular diseases (CVDs): Fact Sheet*. <http://www.who.int/mediacentre/factsheets/fs317/en/>
- CDC. 2016. *At a Glance 2016: Heart Disease and Stroke*. <https://www.cdc.gov/chronicdisease/resources/publications/aag/pdf/2016/aag-heart-disease.pdf>
- NHS. 2016. *Cardiovascular Disease*. <https://www.nhs.uk/conditions/cardiovascular-disease/>
- HSE. 2017. *Cardiovascular Disease*. <http://www.hse.ie/eng/health/az/C/Cardiovascular-disease/>
- World Heart Federation. 2017. *Cardiovascular Risk Factors*. <https://www.world-heart-federation.org/resources/risk-factors/>
- Garcia, Mariana, Sharon L. Mulvagh, C. Noel Bairey Merz, Julie E. Buring, and JoAnn E. Manson. "Cardiovascular disease in women." *Circulation research* 118, no. 8 (2016): 1273-1293.
- Pomp, Elisabeth R., Frits R. Rosendaal, and Carine JM Doggen. "Smoking increases the risk of venous thrombosis and acts synergistically with oral contraceptive use." *American journal of hematology* 83, no. 2 (2008): 97-102.
- Witkowski, Sarah, and Corinna Serviente. "Changing Sex Hormones Represent a Cardiovascular Disadvantage for Aging Women." *Exercise and sport sciences reviews* 45, no. 2 (2017): 57.
- Rosano, G. M. C., I. Spoleitini, and C. Vitale. "Cardiovascular disease in women, is it different to men? The role of sex hormones." *Climacteric* 20, no. 2 (2017): 125-128.
- Stramba-Badiale, Marco, Kim M. Fox, Silvia G. Priori, Peter Collins, Caroline Daly, Ian Graham, Benct Jonsson, Karin Schenck-Gustafsson, and Michal Tendera. "Cardiovascular diseases in women: a statement from the policy conference of the European Society of Cardiology." *European heart journal* (2006): 994-1005.
- Clegg, Deborah, Andrea L. Hevener, Kerrie L. Moreau, Eugenia Morselli, Alfredo Criollo, Rachael E. Van Pelt, and Victoria J. Vieira-Potter. "Sex Hormones and Cardiometabolic Health: Role of Estrogen and Estrogen Receptors." *Endocrinology* 158, no. 5 (2017): 1095-1105.
- dos Santos, Roger Lyrio, Fabricio Bragança da Silva, Rogério Faustino Ribeiro, and Ivanita Stefanon. "Sex hormones in the cardiovascular system." *Hormone molecular biology and clinical investigation* 18, no. 2 (2014): 89-103.
- Norhammar, A., and K. Schenck-Gustafsson. "Type 2 diabetes and cardiovascular disease in women." *Diabetologia* 56, no. 1 (2013): 1-9.
- El Khoudary, Samar R., Kelly J. Shields, Imke Janssen, Carrie Hanley, Matthew J. Budoff, Emma Barinas-Mitchell, Susan A. Everson-Rose, Lynda H. Powell, and Karen A. Matthews. "Cardiovascular fat, menopause, and sex hormones in women: the SWAN Cardiovascular Fat Ancillary Study." *The Journal of Clinical Endocrinology & Metabolism* 100, no. 9 (2015): 3304-3312.
- European Heart Health Strategy. 2009. *Red alert on women's hearts: women and cardiovascular research in Europe*. https://www.escardio.org/static_file/Escardio/EU-Affairs/WomensHearts-RedAlert.pdf
- Stramba-Badiale, Marco, Kim M. Fox, Silvia G. Priori, Peter Collins, Caroline Daly, Ian Graham, Benct Jonsson, Karin Schenck-Gustafsson, and Michal Tendera. "Cardiovascular diseases in women: a statement from the policy conference of the European Society of Cardiology." *European heart journal* (2006): 994-1005.
- Mokdad, Ali H., Earl S. Ford, Barbara A. Bowman, William H. Dietz, Frank Vinicor, Virginia S. Bales, and James S. Marks. "Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001." *Jama* 289, no. 1 (2003): 76-79.
- Stramba-Badiale, Marco, Kim M. Fox, Silvia G. Priori, Peter Collins, Caroline Daly, Ian Graham, Benct Jonsson, Karin Schenck-Gustafsson, and Michal Tendera. "Cardiovascular diseases in women: a statement from the policy conference of the European Society of Cardiology." *European heart journal* (2006): 994-1005.
- Norhammar, A., and K. Schenck-Gustafsson. "Type 2 diabetes and cardiovascular disease in women." *Diabetologia* 56, no. 1 (2013): 1-9.
- De Simone, Giovanni, Richard B. Devereux, Marcello Chinali, Elisa T. Lee, James M. Galloway, Ana Barac, Julio A. Panza, and Barbara V. Howard. "Diabetes and incident heart failure in hypertensive and normotensive participants of the Strong Heart Study." *Journal of hypertension* 28, no. 2 (2010): 353.
- Garcia, Mariana, Sharon L. Mulvagh, C. Noel Bairey Merz, Julie E. Buring, and JoAnn E. Manson. "Cardiovascular disease in women." *Circulation research* 118, no. 8 (2016): 1273-1293.
- Huxley, Rachel, Federica Barzi, and Mark Woodward. "Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies." *Bmj* 332, no. 7533 (2006): 73-78.
- Diabetes UK. 2015. *Diabetes News*. https://www.diabetes.org.uk/about_us/news/gestational-diabetes-and-children
- Perk, Joep, Guy De Backer, Helmut Gohlke, Ian Graham, Željko Reiner, WM Monique Verschuren, Christian Albus et al. "European Guidelines on cardiovascular disease prevention in clinical practice (version 2012)." *International journal of behavioral medicine* 19, no. 4 (2012): 403-488.
- National Institute for Health and Care Excellence. 2015. *Diabetes in pregnancy: management from preconception to the postnatal period*. <https://www.nice.org.uk/guidance/ng3/chapter/2-research-recommendations#postnatal-treatment-for-women-diagnosed-with-gestational-diabetes>
- European Heart Health Strategy. 2009. *Red alert on women's hearts: women and cardiovascular research in Europe*. https://www.escardio.org/static_file/Escardio/EU-Affairs/WomensHearts-RedAlert.pdf

52. Mayo Clinic. 2017. *Heart Disease*. <https://www.mayoclinic.org/diseases-conditions/heart-disease/symptoms-causes/syc-20353118>
53. WHO. 2017. *Cardiovascular diseases (CVDs): Fact Sheet*. <http://www.who.int/mediacentre/factsheets/fs317/en/>
54. Stramba-Badiale, Marco, Kim M. Fox, Silvia G. Priori, Peter Collins, Caroline Daly, Ian Graham, Benct Jonsson, Karin Schenck-Gustafsson, and Michal Tendera. "Cardiovascular diseases in women: a statement from the policy conference of the European Society of Cardiology." *European heart journal* (2006): 994-1005.
55. Regitz-Zagrosek, Vera, Sabine Oertelt-Prigione, Eva Prescott, Flavia Franconi, Eva Gerdt, Anna Foryst-Ludwig, Angela HEM Maas et al. "Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes." *European heart journal* 37, no. 1 (2016): 24-34.
56. Harvard Health Publishing. 2017. *Gender matters: Heart disease risk in women*. <https://www.health.harvard.edu/heart-health/gender-matters-heart-disease-risk-in-women>
57. Diercks, Deborah B., Kelly P. Owen, Michael C. Kontos, Andra Blomkalns, Anita Y. Chen, Chadwick Miller, Stephen Wiviott, and Eric D. Peterson. "Gender differences in time to presentation for myocardial infarction before and after a national women's cardiovascular awareness campaign: A temporal analysis from the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation (CRUSADE) and the National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network—Get with the Guidelines (NCDR ACTION Registry—GWTG)." *American heart journal* 160, no. 1 (2010): 80-87.
58. Kaul, Padma, Paul W. Armstrong, Sunil Sookram, Becky K. Leung, Neil Brass, and Robert C. Welsh. "Temporal trends in patient and treatment delay among men and women presenting with ST-elevation myocardial infarction." *American heart journal* 161, no. 1 (2011): 91-97.
59. Dallongeville, Jean, Dirk De Bacquer, Jan Heidrich, Guy De Backer, Christoph Prugger, Kornelia Kotseva, Michèle Montaye, and Philippe Amouyel. "Gender differences in the implementation of cardiovascular prevention measures after an acute coronary event." *Heart* 96, no. 21 (2010): 1744-1749.
60. Piepoli, Massimo F., Arno W. Hoes, Stefan Agewall, Christian Albus, Carlos Brotons, Alberico L. Catapano, Marie-Therese Cooney et al. "2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)." *European heart journal* 37, no. 29 (2016): 2315-2381.
61. Musselman, Dominique L., Dwight L. Evans, and Charles B. Nemeroff. "The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment." *Archives of general psychiatry* 55, no. 7 (1998): 580-592.
62. Lichtman, Judith H., James A. Blumenthal, Nancy Frasure-Smith, Peter G. Kaufmann, François Lespérance, Daniel B. Mark, David S. Sheps, C. Barr Taylor, and Erika Sivarajan Froelicher. "Depression and coronary heart disease." *Circulation* 118, no. 17 (2008): 1768-1775.
63. Ladwig, K.H., Lederbogen, F., Albus, C., Angermann, C., Borggrefe, M., Fischer, D., Fritzsche, K., Haass, M., Jordan, J., Jünger, J. and Kindermann, I., 2014. Position paper on the importance of psychosocial factors in cardiology: update 2013. *GMS German Medical Science*, 12.
64. Ford, Earl S., and Simon Capewell. "Coronary heart disease mortality among young adults in the US from 1980 through 2002." *Journal of the American College of Cardiology* 50, no. 22 (2007): 2128-2132.
65. Kuklina, Elena V., Carma Ayala, and William M. Callaghan. "Hypertensive disorders and severe obstetric morbidity in the United States." *Obstetrics & Gynecology* 113, no. 6 (2009): 1299-1306.
66. Duley, Lelia. 2009. The global impact of pre-eclampsia and eclampsia. In *Seminars in perinatology*, vol. 33, no. 3: 130-137.
67. Hughes, Sue. "Heart Disease Is Lead Cause of Death in Pregnancy." *Medscape*, September 13, 2012. <https://www.medscape.com/viewarticle/770901>.
68. Bellamy, L., Casas, J.P., Hingorani, A.D. and Williams, D.J., 2007. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *Bmj*, 335(7627), p.974.
69. Bushnell, Cheryl, Louise D. McCullough, Issam A. Awad, Monique V. Chireau, Wende N. Fedder, Karen L. Furie, Virginia J. Howard et al. "Guidelines for the prevention of stroke in women." *Stroke* 45, no. 5 (2014): 1545-1588.
70. Kaemmerer, Mathias, Matthäus Vigl, Vanadin Seifert-Klauss, Nicole Nagdyman, Ulrike Bauer, Karl-Theo Maria Schneider, and Harald Kaemmerer. "Counseling reproductive health issues in women with congenital heart disease." *Clinical Research in Cardiology* 101, no. 11 (2012): 901-907.
71. HSE. 2017. *Hormone Replacement Therapy (HRT)*. <http://www.hse.ie/eng/health/az/H/Hormone-replacement-therapy-HRT/>
72. Mayo Clinic. 2017. *Hormone Replacement Therapy and Your Heart*. <https://www.mayoclinic.org/diseases-conditions/menopause/in-depth/hormone-replacement-therapy/art-20047550>
73. Maclaran, Kate, and John C. Stevenson. "Primary prevention of cardiovascular disease with HRT." *Women's Health* 8, no. 1 (2012): 63-74.
74. Mayo Clinic. 2017. *Hormone Replacement Therapy and Your Heart*. <https://www.mayoclinic.org/diseases-conditions/menopause/in-depth/hormone-replacement-therapy/art-20047550>
75. Schierbeck, Louise Lind, Lars Rejnmark, Charlotte Landbo Tofteng, Lis Stilgren, Pia Eiken, Leif Mosekilde, Lars Køber, and Jens-Erik Beck Jensen. "Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial." *Bmj* 345 (2012): e6409.
76. Hickey, Martha, Jane Elliott, and Sonia Louise Davison. "Hormone replacement therapy." *BMJ* 344 (2012): e763.
77. WHO. 2007. *Prevention of cardiovascular disease: guidelines for assessment and management of cardiovascular risk*. http://www.who.int/cardiovascular_diseases/guidelines/Full%20text.pdf
78. Yang, Xiao-Ping, and Jane F. Reckelhoff. "Estrogen, hormonal replacement therapy and cardiovascular disease." *Current opinion in nephrology and hypertension* 20, no. 2 (2011): 133.
79. Mosca, Lori, Lawrence J. Appel, Emelia J. Benjamin, Kathy Berra, Nisha Chandra-Strobo, Rosalind P. Fabunmi, Deborah Grady et al. "Evidence-based guidelines for cardiovascular disease prevention in women." *Arteriosclerosis, thrombosis, and vascular biology* 24, no. 3 (2004): e29-e50.
80. Harman, S. Mitchell, Eric Vittinghoff, Eliot A. Brinton, Matthew J. Budoff, Marcelle I. Cedars, Rogerio A. Lobo, George R. Merriam et al. "Timing and duration of menopausal hormone treatment may affect cardiovascular outcomes." *The American journal of medicine* 124, no. 3 (2011): 199-205.
81. Harman, S. Mitchell, Eric Vittinghoff, Eliot A. Brinton, Matthew J. Budoff, Marcelle I. Cedars, Rogerio A. Lobo, George R. Merriam et al. "Timing and duration of menopausal hormone treatment may affect cardiovascular outcomes." *The American journal of medicine* 124, no. 3 (2011): 199-205.
82. Kim, Esther SH, Thomas P. Carrigan, and Venu Menon. "Enrollment of women in National Heart, Lung, and Blood Institute-funded cardiovascular randomized controlled trials fails to meet current federal mandates for inclusion." *Journal of the American College of Cardiology* 52, no. 8 (2008): 672-673.
83. Stramba-Badiale, Marco. "Women and research on cardiovascular diseases in Europe: a report from the European Heart Health Strategy (EuroHeart) project." *European heart journal* 31, no. 14 (2010): 1677-1681.
84. Buttar, Harpal S., Timao Li, and Nivedita Ravi. "Prevention of cardiovascular diseases: Role of exercise, dietary interventions, obesity and smoking cessation." *Experimental & Clinical Cardiology* 10, no. 4 (2005): 229.
85. WHO. 2012. *Action Plan for implementation of the European Strategy for the Prevention and Control of Noncommunicable Diseases 2012–2016*. http://www.euro.who.int/_data/assets/pdf_file/0019/170155/e96638.pdf?ua=1
86. European Commission. 2017. *Tobacco policy*. https://ec.europa.eu/health/tobacco/policy_en
87. European Commission. 2017. *EU anti-tobacco campaigns*. https://ec.europa.eu/health/tobacco/ex_smokers_are_unstoppable_en
88. European Commission. 2017. *Major and Chronic Diseases: Cardiovascular Disease*. https://ec.europa.eu/health/major_chronic_diseases/diseases/cardiovascular_en
89. European Heart Network. 2017. *About Us*. <http://www.ehnheart.org/>
90. European Society of Cardiology. 2017. *European Heart Health Charter*. <https://www.escardio.org/The-ESC/Advocacy/Shaping-policy-and-regulation/European-Heart-Health-Charter>
91. European Health Charter. 2007. *Read the Charter*. <http://www.heartcharter.org/read-charter/part-2.aspx>
92. European Commission. 2017. *Research Areas: Cardiovascular*. <https://ec.europa.eu/research/health/index.cfm?pg=area&areaname=cardiovascular>