

Kristina Orth-Gomér
Neil Schneiderman
Viola Vaccarino
Hans-Christian Deter
Editors

Psychosocial Stress and Cardiovascular Disease in Women

Concepts, Findings, Future Perspectives

 Springer

Psychosocial Stress and Cardiovascular Disease in Women

Kristina Orth-Gomér • Neil Schneiderman
Viola Vaccarino • Hans-Christian Deter
Editors

Psychosocial Stress and Cardiovascular Disease in Women

Concepts, Findings, Future Perspectives

 Springer

Editors

Kristina Orth-Gomér
Department of Clinical Neuroscience
Karolinska Institute
Stockholm, Sweden

Neil Schneiderman
Department of Psychology
University of Miami
Coral Gables, FL, USA

Viola Vaccarino
Department of Epidemiology
Rollins School of Public Health Emory
University
Atlanta, GA, USA

Hans-Christian Deter
Department of Psychosomatic Medicine,
Charité University Medicine
Campus Benjamin Franklin
Berlin, Germany

ISBN 978-3-319-09240-9

ISBN 978-3-319-09241-6 (eBook)

DOI 10.1007/978-3-319-09241-6

Springer Cham Heidelberg New York Dordrecht London

Library of Congress Control Number: 2014945743

© Springer International Publishing Switzerland 2015

This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed. Exempted from this legal reservation are brief excerpts in connection with reviews or scholarly analysis or material supplied specifically for the purpose of being entered and executed on a computer system, for exclusive use by the purchaser of the work. Duplication of this publication or parts thereof is permitted only under the provisions of the Copyright Law of the Publisher's location, in its current version, and permission for use must always be obtained from Springer. Permissions for use may be obtained through RightsLink at the Copyright Clearance Center. Violations are liable to prosecution under the respective Copyright Law.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

While the advice and information in this book are believed to be true and accurate at the date of publication, neither the authors nor the editors nor the publisher can accept any legal responsibility for any errors or omissions that may be made. The publisher makes no warranty, express or implied, with respect to the material contained herein.

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Words of Guidance from the Past President of Karolinska Institutet, Sweden

Even though Sweden is one of the countries in the world where work with equality has progressed pretty far, it is still necessary for us to focus on the situation of women in society. We know that negative stress has a detrimental effect on health. And we know that it is not always easy to avoid stress.

Throughout the ages, and still today, women have generally taken greater responsibility for the home and the family. But even though women do most of the work in the home, investigations show that they have a greater feeling of insufficiency than men have. Women, quite simply, become more stressed than men when they don't have as much time for the family as they would like.

A fundamental initiative promoting equality in the home may be one method of reducing in the long term the stress to which women are subject. But times are changing. Even as the stress structures from the past remain in place, new ones arrive.

A recent study published in March of 2012 has shown that the new social medium "Facebook" causes us to feel bad and creates negative stress. And again, it is women who are most affected, and experience the greatest stress. The study did not give a clear answer about why women are stressed by "Facebook" more than men are, but we can speculate.

"Facebook" is, after all, a way of displaying yourself and your life. Many investigations, including the one I just referred to, show that "Facebook" users tend to embellish their presentations. People write most about what is positive, and they only put up images that show a happy person with a happy family. And that's not really so strange. It's what we do in real life as well. If you listen to the chat during coffee breaks at work, you will hear more stories of successful weekend activities than you will hear about failure and drama.

And just as we are influenced by colleague's chat at work, we are influenced by what they write on "Facebook." Many compare their own life with what they hear, and wonder how happy they really are, in the light of the amazing successes of others. And it's very probable that this can produce negative stress.

But why are women more stressed by others' successes than men? Let us go back to equality at home. Women experience more stress than men when they find it impossible to combine work and family in a satisfactory manner. Why is this?

It may be that women often place higher demands on themselves than men do, and for this reason find it easier to feel a failure when compared with others. “Facebook” works in the same way. Continual reminders of successful friends create negative stress in women whose ambition is to succeed in all areas of life.

One way of reducing the negative stress that often affects women, therefore, may be to work with women’s self-image and the demands they place on themselves. This, it can be hoped, will reduce the negative stress and improve women’s health in the long run.

Still today, women receive poorer health care than men. There are probably many explanations for this, and one of them, of course, is that so many more scientists in the medical field have been men than women for so long. And the patients on whom research was carried out were often mainly men. So it’s not so unexpected that many aspects of health care have been based on the preconditions of men. But we now know that there are large differences between men and women when it comes to their needs for high-quality health care. One example that has received attention in recent years is that men and women display different symptoms during a heart attack.

Development within medical research does not take place on an isolated island, but against the background of the general development of society. Few of us believe that male dominance in medical research is due to men being more gifted than women. It is, of course, due to that fact that women have had to fight so much harder to advance within the academic world. And they have had to fight not only against prejudice, but also against structural obstacles that have been placed in the pathway of just women.

When Karolinska Institutet was formed 200 years ago, it was intended right from the start that it would be more modern and innovative than the traditional universities. For that reason, it was decided as early as around 1900 that women would be allowed at the university, but only if they remained unmarried. A woman who got married was compelled to end her studies.

It is easy to understand that the few women who chose to study at Karolinska Institutet during this period found themselves in impossible dilemmas. And, it’s worth asking how many male students and scientists we would have had if it had been a requirement that men deny themselves a traditional family life with a wife and children in order to be allowed to study and carry out research.

I’ve given these examples to illustrate and explain why men have dominated medical research for so long, using the male body as the starting point of their research.

But you can’t stop progress, even if progress is slow. Women are catching up. Today 60 % of the research students at Karolinska Institutet are women. And it is a requirement for being awarded a research grant for a study that both men and women patients are included.

I hope that within the not too distant future we will obtain so much knowledge about the differences between men and women that everyone will receive optimal treatment, independent of gender.

Harriet Wallberg-Henriksson

Preface

This book represents a collective effort to summarize the findings of two decades of research on psychosocial aspects of women's cardiovascular disease.

Today's scientific, psychosocial, and behavioral medicine knowledge base is increasing exponentially. In fact, the literature is so large, that it has become difficult to grasp. For example in the field of psycho-cardiology, several thousand papers on stress and heart disease have been published during the past two decades. Nevertheless almost all of this literature has been focused on men. It was believed—for a long time—that coronary heart disease was a man's illness. Women were thought to be virtually immune, at least in younger ages.

There are a fair number of clinical case reports from patients, who have been told, in their contacts with hospitals and health care, that their symptoms of chest pain could not possibly come from the heart.

“Women of your age simply do not get heart disease” was the comment from the nurse at the emergency room of a large Stockholm University Hospital, to a woman patient who came to the acute cardiology clinic because of severe chest pain. She had first gone to see her medical officer at the occupational medicine department of her work place. There she was reassured that her symptoms came from her low back musculature, and that they would subside with rest and warmth.

Instead they grew worse. On the second day, she went back to the emergency room. She went in her own car, as the waiting time for emergency transportation seemed awfully long. After all she had been told it was only low back pain. This time an electrocardiogram (ECG) was recorded, which showed pathological changes, typical of an acute myocardial infarction. The patient was immobilized, put to bed, and not allowed to get up for the next 24 h.

Through these and other experiences, the quality of care for women with cardiac disease has been questioned. A large body of interest has been focused on the inequality issue in the healthcare system. Women have been shown to be disadvantaged in the use of coronary interventions. This seems to be particularly true for older women.

This book is divided into three main parts:

1. Epidemiology and risk factors
2. Mechanisms
3. Clinical Interventions

Part I deals with epidemiology and coronary risk factors. That heart disease in women is an enormous problem is convincingly shown by Sara P. Wamala. This non-communicable disease, as named by the WHO, is the number one killer among women and men throughout the whole world.

On a national and international level these basic epidemiological issues are discussed by Annika Rosengren and Karin Manhem, Göteborg, in their chapter in Part I. Both have a solid experience and an impressive publication list concerning heart diseases, especially their risk profile in women. Also the publication issue of the skewed age distribution with many more female patients in the older than in the younger patient groups in published papers is discussed in their chapter. One consequence of the uneven age distribution is the difficulty to identify a sufficient number of female patients in the young and productive ages, under 65. This small group of patients has attracted much interest. Nanette Wenger, experienced cardiologist and frequently cited epidemiologist feels that standard physiological risk factors could explain the poor prognosis of young women with heart disease.

The psychosocial risk profiles of these women are underlined in the following chapters by Diana Chirinos and Neil Schneiderman, who focus on depression and Viola Vaccarino, who has a special focus on posttraumatic stress. She points out that the earlier life experiences of women patients often are forgotten. They need to be taken into account, as they continue to influence health throughout life.

One chapter of this section is focused on women's experience of multiple conflicting stressors, such as between work and family roles and related issues. Orth-Gomér and collaborators, Sarah Wamala, Myriam Horsten, May Blom, Constance Leineweber, and Birgitta Lindvall have worked extensively with this topic. The group is known for their work on women's "marital stress" as a predictor of recurrent cardiac events. The first paper on this topic concerned Stockholm women, and appeared in December 2000. There were several ideas about interventions. One American colleague called and offered transatlantic marriage counselling in the CCU as a Christmas gift to our patients.

In Part II we describe available knowledge on psycho-biological mechanisms that mediate the effects of psychosocial disturbances on the disease process.

A large amount of knowledge is presented from mal-adaptation, dysfunction, and imbalance of the sympathetic/parasympathetic nervous system by Töres Theorell, to recovery and restitution of health, through sleep, by Johanna Schwarz, Eva Lindberg, and Goran Kecklund. These are well-known and experienced psychosocial researchers. Reflected in their chapters is a vast experience with both basic research and implementation of psychosocial findings. The important immunological pathway is skillfully disentangled by Paula Mommersteg and Wijo Kop, who started his career in Maastricht, extended his scientific activities to the USA and became editor in chief of "Psychosomatic Medicine," but is now back in the Netherlands, at the Tilburg

University. Douglas Bremner provides his profound interest and valuable knowledge in Neurobiology in particular the neurobiological consequences of posttraumatic stress disorder (PTSD). Co-authoring with Viola Vaccarino they demonstrate by epidemiologic and neuroscientific evidence the importance of the posttraumatic stress disorder. The ever posed and seldom answered question on how much of causality can be explained by genes, and how much by the environmental influences is elegantly described by Redford Williams of the Duke University, USA. In a scholarly presentation he explains the complex interactions between psychological, social, physical, and genetic influences.

Part III deals with clinical interventions from a number of different programs important for women with CHD. One can learn how to breathe more effectively, and how to lower blood pressure, while being inspired by Margaret A. Chesney and David Anderson. The core life skills are effectively taught by Virginia Williams to both men and women. Both genders benefit, but for different reasons.

Psychodynamic qualities are introduced for the first time in psychosocial interventions in German programs like SPIRR-CAD (Stepwise Intervention to reduce risk in Coronary Artery Disease) and BAT (Berlin Anxiety Trial). The common focus as reported by Hans-Christian Deter, Charite University Medicine, Berlin, is on improving coping strategies, regulating emotions, mainly anxiety and depression and enhancing personal interactions. Finally Neil Schneiderman et al. discusses the most recent and conclusive cognitive intervention models for women's heart disease. They challenge some of the "old truths," advocating that men and women form separate treatment groups, that patients are not recruited before 6 weeks have passed post hospitalization, which means they have left their most acute phase and began recovery, The program should be modeled according to patient needs, with special attention paid to patient adherence. The SWITCHD (the Stockholm Women Intervention Trial for Coronary Heart Disease) stress reduction program, that was able to reduce mortality in women with heart disease, was designed in this way and initiated upon collective demand from women patients. It was the very source of inspiration and the spur of this whole book. Together with the similar results from the SUPRIM study in Uppsala, the evidence of psychosocial causation, mechanisms, and preventative efforts begin to make sense.

The combined knowledge base and novel scientific methodology, inherent in psychosomatic, psychosocial, and behavioral medicine are necessary elements for successful intervention and prevention. But we also need basic core competence in medicine, cardiology, psychology, and other areas of the natural and human life sciences.

Stockholm, Sweden
May 2014

Kristina Orth-Gomér

Acknowledgments

The manuscripts of this book were skillfully coordinated by Lillemor Katz, Karolinska Institutet, Stockholm, with competent assistance from the department of scientific illustrations at Charité University Medicine, Berlin and from Janice Stern of Springer Publishing Company, New York City. The editors express their special thanks to all co-authors, who took so much of their time and interest to submit excellent overviews of their respective fields. The editors are also grateful to all women patients, who volunteered their time and interest to provide a wealth of data, from reports of life stress, to 24 h ambulatory ECG monitoring, to invasive angiographic examinations and re-examinations.

Financial support was obtained from the Swedish Labor Market Insurance Company, AFA, from the Swedish Medical and Social Sciences Research Councils, the Heart and Lung Foundation, the Osher Foundation, Karolinska Institutet, the Stockholm County Council, and the US National Institutes of Health RO1 HL45 785, R01 HL109413 and R01 HL088726.

We are also grateful for scientific exchange, advice, and guidance from international organizations, including the American Society of Psychosomatic Medicine and the International Society of Behavioral Medicine.

Contents

Part I Epidemiology and Risk Factors

- 1 **Enhancing Women's Heart Health from a Global Perspective** 3
Sarah P. Wamala
- 2 **Epidemiology and Standard Risk Factors in Relation to Psychosocial Risk Factors for Coronary Heart Disease**..... 7
Annika Rosengren and Karin Manhem
- 3 **Coronary Heart Disease in Women: Evolution of Our Knowledge** 13
Nanette Kass Wenger
- 4 **Psychosocial Risk Factors for Coronary Heart Disease in Women: The Stockholm Studies of Women's Hearts**..... 27
Kristina Orth-Gomér
- 5 **Depression and Cardiovascular Disease in Women: Behavioral and Biological Mechanisms Involved in this Association** 41
Diana A. Chirinos and Neil Schneiderman
- 6 **Psychosocial Risk Factors in Women: Special Reference to Depression and Posttraumatic Stress Disorder**..... 63
Viola Vaccarino

Part II Psycho-biological Mechanisms and Pathways

- 7 **On Basic Physiological Stress Mechanisms in Men and Women: Gender Observations on Catecholamines, Cortisol and Blood Pressure Monitored in Daily Life** 89
Töres Theorell

8 Sleep as a Means of Recovery and Restitution in Women: The Relation with Psychosocial Stress and Health 107
 Johanna Schwarz, Eva Lindberg, and Goran Kecklund

9 Psychoneuroimmunological Pathways and Sex Differences in Coronary Artery Disease: The Role of Inflammation and Estrogen..... 129
 Willem J. Kop and Paula M.C. Mommersteeg

10 Gene by Environment Interactions: Impact on Women’s Health..... 151
 Redford B. Williams

11 Neurobiology of Early Life Stress in Women 161
 J. Douglas Bremner and Viola Vaccarino

Part III Clinical Interventions

12 Inhibited Breathing and Salt-Sensitive Hypertension in Women..... 181
 David E. Anderson and Margaret A. Chesney

13 “Lifeskills” Training: Both Women and Men Benefit—But for Different Reasons..... 197
 Virginia Williams

14 Cognitive Programs, Dynamic Concepts, and Interpersonal Relations: Some Results of the Berlin Anxiety Clinical Trial..... 209
 Hans-Christian Deter

15 Gender Considerations in Psychosocial–Behavioral Interventions for Coronary Heart Disease 233
 Neil Schneiderman, Kristina Orth-Gomér, and Gunilla Burell

16 How Did the Stress Reduction Program Help Women to Survive? The Patient’s View in the SWITCHD Study 251
 May Blom, Hans-Christian Deter, and Kristina Orth-Gomér

17 Summary, Conclusions and Future Directions of Research..... 261
 Kristina Orth-Gomér and Hans-Christian Deter

Common Abbreviations..... 283

Author Index..... 285

Subject Index..... 295

Contributors

David E. Anderson, Ph.D. Division of Neurology, Department of Medicine, University of California, San Francisco, CA, USA

May Blom, Ph.D., R.N. Stockholm County Council, Stockholm, Sweden

J. Douglas Bremner, M.D. Department of Psychiatry and Behavioral Sciences, Emory School of Medicine, Atlanta, GA, USA

Gunilla Burell, Ph.D. Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden

Margaret A. Chesney, Ph.D. Department of Medicine, Osher Center for Integrative Medicine, San Francisco, CA, USA

Diana A. Chirinos, M.S. Health Clinical Psychology, University of Miami, Miami, FL, USA

Hans-Christian Deter, M.D. Department of Psychosomatic Medicine, Charité University Medicine, Campus Benjamin Franklin, Berlin, Germany

Goran Kecklund, Ph.D. Stress Research Institute, Stockholm University, Stockholm, Sweden

Willem J. Kop, Ph.D. Department of Medical and Clinical Psychology, Center of Research on Psychology in Somatic disease (CoRPS), Tilburg University, Tilburg, The Netherlands

Eva Lindberg, M.D. Department of Medical Sciences, Respiratory Medicine and Allergology, Uppsala University, Uppsala, Sweden

Karin Manhem, M.D., Ph.D. Department of Molecular and Clinical Medicine, University of Gothenburg, Gothenburg, Sweden

Melanie Merswolken, D.M.Sc. Department of Psychosomatic Medicine, Campus Benjamin Franklin, Charité–Universitätsmedizin, Berlin, Berlin, Germany

Paula M.C. Mommersteeg, Ph.D. Center of Research on Psychology in Somatic disease (CoRPS), Tilburg University, Tilburg, The Netherlands

Kristina Orth-Gomér, M.D., Ph.D. Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden

Annika Rosengren, M.D. Department of Cardiology and Epidemiology, Sahlgrenska Academy, Gothenburg, Sweden

Neil Schneiderman, Ph.D. Behavioral Medicine Unit, University of Miami, Miami, FL, USA

Johanna Schwarz, Ph.D. Department of Psychology and Stress Research Institute, Stockholm University, Stockholm, Sweden

Töres Theorell, M.D. Stress Research Institute, Stockholm University, Stockholm, Sweden

Viola Vaccarino, M.D., Ph.D. Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta, GA, USA

Christina Walldin R.N. Stockholm County Council, Stockholm, Sweden

Harriet Wallberg-Henriksson, M.D. Karolinska Institutet, Stockholm, Sweden

Sarah P. Wamala, Ph.D. Karolinska Institutet, Stockholm, Sweden

Nanette Kass Wenger, M.D., M.A.C.C., M.A.C.P., F.A.H.A. Department of Medicine, Division of Cardiology, Emory University School of Medicine, Atlanta, GA, USA

Redford B. Williams, M.D. Duke University Medical Center, Durham, NC, USA

Virginia Williams, Ph.D. Williams LifeSkills Inc., Durham, NC, USA

Part I
Epidemiology and Risk Factors

Chapter 1

Enhancing Women's Heart Health from a Global Perspective

Sarah P. Wamala

Abstract Coronary heart disease (CHD) is the most common cause of death among men and women. Whereas Europe incidence mortality rates are decreasing, in the third world they are increasing, possibly as a result of improved economy and welfare. The lifestyles worsen and CHD rates increase progressively. There is an urgent need for action to avoid an epidemic in the third world.

Keywords Coronary heart disease (CHD) • Women • Global perspective • Noncommunicable (NCD) • Enhancement of heart health

The Challenge of Noncommunicable Diseases

Noncommunicable diseases (NCDs), which include cardiovascular diseases, contribute to 63 % of mortality globally. Much as NCDs have been associated with affluent societies of the high income countries, the fact is that 80 % of mortality due to NCDs occurs in low and middle income countries (WHO). NCDs will continue to be a global public health challenge due to the fact that 29 % mortality occurs in persons below 60 years of age. The cardiovascular risk factors are present in an increasingly large proportion of the young generations. Cardiovascular diseases (CVDs) account for most NCD deaths, about 17.3 million people annually, followed by cancers (7.6 million), respiratory diseases (4.2 million), and diabetes (1.3 million) (The World Health Organization 2011).

The burden of NCDs is not only associated with human suffering but also with economic consequences. Every 10 % increase in the prevalence of NCDs is associated with 0.5 % decrease in annual economic growth. These costs are estimated to increase over the next two decades, costing as much as US\$47 trillion (The World Economic Forum and the Harvard School of Public Health 2011). In Sweden alone, tobacco use, alcohol consumption, physical inactivity, and unhealthy eating habits are estimated to cost the society about 6 billion euros per year (Linell et al. 2013).

S.P. Wamala, Ph.D. (✉)
Karolinska Institutet, Stockholm, Sweden
e-mail: swamala8@gmail.com

The UN High-Level Meeting on NCDs in 2011 marked the beginning of an increased global focus and a growing political commitment at a high level to take urgent action on NCDs (UN summit, New York, September 2011).

The WHO has taken further steps including demonstrating an overview of the global burden of NCDs and providing a WHO action plan for the prevention and control of NCDs 2013–2020 (The World Health Organization 2013a, b). Both the curative and mainly the preventive strategies are needed. Prevention of unhealthy lifestyles can reduce 75 % of CVD, stroke, type-2 diabetes, and 40 % of cancers (The World Health Organization 2011).

Coronary Heart Disease and Gender

The epidemiologic evidence of NCDs indicates that coronary heart disease (CHD) is the largest contributor to social disparities in disability and premature death. Women are particularly vulnerable to CHD given the social, gender, and economic inequalities that create inequities in access to critical health services (including prevention), exposures to various risk factors, health information, health-promoting and life-saving resources (Wamala and Lynch 2002).

According to the World health statistics 2013, ischemic heart disease and stroke are the top 10 leading causes of death for women in the world (The World Health Organization 2013a, b). The pattern is similar in different regions even after stratifying by level of economic development, with the exception of low income regions where lower respiratory infections and HIV/AIDS are still the top leading causes of death. The low income regions in fact face the double burden of communicable and noncommunicable diseases. The World Heart Federation estimates that over 8.6 million women globally die of heart disease and stroke each year, which is more than the total number of women who die from all cancers, tuberculosis, HIV/AIDS and malaria combined (<http://www.world-heart-federation.org/what-we-do/awareness/go-red-for-women/> accessed on 2nd January 2014).

The WHO demonstrates that men slightly outnumber women globally, but, as women tend to live longer than men, they represent a higher proportion of older adults: 54 % of people 60 years of age and older are women, a proportion that rises to almost 60 % at age 75 and older, and to 70 % at age 90 and older (<http://www.who.int/mediacentre/factsheets/fs334/en/> accessed on 2nd January 2014). It is also worth noting that although the rate of death from CHD has declined over the past decades, the rates are actually increasing in younger women due to a variety of risk factors.

For example, in Stockholm women patients with CHD (acute or pending myocardial infarction), those who reported intense periods of stress in family life were prospectively shown to have a threefold increased 5-year incidence of recurrent cardiac, fatal and nonfatal, events (Orth-Gomér et al. 2002). These women had asked the researchers for a specific educational program to help them cope with stress in family life. In response to their demand, in a randomized clinical trial, the researchers initiated a new project, “Healthier Female Hearts.” Stockholm women

with CHD received a 1-year cognitive behavioral intervention, which improved coping and lifestyle. This program also had a remarkable long-term effect: their mortality decreased; they not only lived longer, they also had a better quality of life (Orth-Gomer et al. 2009).

NCDs, particularly CVDs and cancers, are the biggest causes of death among older women globally. CVDs account for 46 % of older women's deaths globally. Cumulative exposure to risk factors in adolescence and adulthood, most of which are related to CVDs reflect most of the health problems faced by women as they get older (<http://www.who.int/mediacentre/factsheets/fs334/en/> accessed on 2nd January 2014).

There is a growing etiologic research on gender differences related to CHD, but limited interventions research that can provide guidelines on how to prevent unnecessary burden of CHD among women. Also there is limited but growing evidence on differentials of effects of risk factors, differentials in the physiology of the cardiovascular system, differentials in survival chances after the first episode of the CHD.

Concluding Remarks

More research to address gender disparities in cardiovascular disease is needed, particular that which addresses effective interventions and policies that can effectively enhance women's heart health. A political commitment to implement the Global Strategy for NCDs and its Action Plan, as well laid out well by the UN and the WHO needs to be taken on seriously by national political leaders. The development of the national targets and indicators based on guidance provided by WHO, should not omit to address gender disparities.

Prevention will give the best gains—saving life and saving money, thus it should be given the highest priority. The health systems need to be strengthened to support primary care, prioritize early detection and treatment, and improve access to affordable essential treatment for heart disease. Additionally the health systems need to be aware of and tackle gender disparities in heart health. In addition to strengthening health systems, global health policies need to be adopted and implemented at national and local levels. Here effective implementation of the WHO framework convention on tobacco control, the Global Strategy on diet, physical activity and health, and the Global Strategy to reduce the harmful use of alcohol provide a good start point. However these strategies need to address gender disparities much more than they do at present.

Advocacy is still needed to increase awareness among health care professionals and providers, decision makers and women themselves. Finally a continued strong global public health community addressing the issues raised above is needed to provide momentum for the work done by the national and local stakeholders. Nevertheless, I dare to say that the WHO's global NCD targets for 2025 will not be achieved without distinctly addressing the social and gender disparities.

References

- Linell, A., Richardson, M. X., & Wamala, S. (2013). The Swedish national public health policy report 2010. *Scandinavian Journal of Public Health*, 41(10 Suppl), 3–56.
- Orth-Gomér, K., Schneiderman, N., & Wang, H. X. (2009). Stress reduction prolongs life in women with coronary disease: The Stockholm Women's Intervention Trial for Coronary Heart Disease (SWITCHD). *Circulation. Cardiovascular Quality and Outcomes*, 2(1), 25–32.
- Orth-Gomér, K., Wamala, S., Horsten, M., Schenck-Gustafsson, K., Schneiderman, N., & Mittleman, M. A. (2002). Marital stress worsens prognosis in women with coronary heart disease. The Stockholm Female Coronary Risk Study. *Journal of the American Medical Association (JAMA)*, 284, 3008–3014.
- The World Economic Forum and the Harvard School of Public Health (2011). *The global economic burden of non-communicable diseases*.
- The World Health Organization (2011). *Global status report on non-communicable diseases 2010*.
- The World Health Organization (2013a). *2008–2013 Action plan for the global strategy for the prevention and control of non-communicable diseases*.
- The World Health Organization. (2013b). *World health statistics 2013. A wealth of information on global public health*. Geneva, Switzerland: Author.
- Wamala, S. P., & Lynch, J. (Eds.). (2002). *Gender and social inequities in health. A public health issue*. Lund, Sweden: Studentlitteratur.

Chapter 2

Epidemiology and Standard Risk Factors in Relation to Psychosocial Risk Factors for Coronary Heart Disease

Annika Rosengren and Karin Manhem

Abstract Women die from coronary heart disease as often as men, but they get the disease about 10 years later in life. Nine coronary risk factors predict almost all of the cases. Among them are smoking, nutrition, lack of exercise, and psychosocial factors, including stress at work and in the family, negative life event, lack of control, deficient social networks, low socio-economic status and depression.

Keywords Coronary heart disease (CHD) • Standard risk factors • Psychosocial risk factor • Atherosclerosis • Acute coronary syndrome • Microvascular disease • Epidemiology

One of two deaths in Europe can be ascribed to cardiovascular disease (CVD), and a third of men and one in four of women who die before age 65, die from CVD. The main background of these clinical manifestations is to be found in the circulatory system, the main task of which is to provide oxygen and energy to bodily organs. The organs are reached through arterial vessels to and venous vessels from the organs. The most common disorders of the vessel wall are due to the pathogenic processes associated with atherosclerosis and with hypertension.

The morphological changes of the artery wall have been examined and described in various kinds of animal and human studies. They have been subject to both experimental and observatory studies. The relevant research fields range from molecular biology to public health. The methodologies and study subjects range from paper and pencil surveys of thousands of men and women, who are examined in large cohorts, to cellular mechanisms, which mediate the atherosclerotic processes in the vessel wall.

A. Rosengren, M.D. (✉)

Department of Cardiology and Epidemiology, Sahlgrenska Academy, Gothenburg, Sweden

K. Manhem, M.D., Ph.D.

Department of Molecular and Clinical Medicine, University of Gothenburg, Gothenburg, Sweden

CVD is the disease, which is the number one killer in all countries, not only in the Western world but lately also in developing nations of the third world.

In epidemiology and public health, both prevalence and incidence figures are central.

In addition the concept of “risk factors” is crucial.

Risk factors have been shown to be statistical predictors of CVD, thus they have been observed to precede the clinical manifestations of CVD. However, they should not be confused with true causal factors, for that role they would have to be demonstrated as causal in experimental studies.

Atherosclerosis starts early in life. In a postmortem study of young Americans, who died from external causes, relatively advanced atherosclerotic changes were seen in the coronary arteries. These were found in a small proportion of men, already in their teen age years. In the age group 30–34 years such changes were observed in, every fifth man. In women of the same age, 1 out of 12 had coronary artery changes, which were indicative of an atherosclerotic process (McGill et al. 2000).

Although these vessel wall changes were observed in early age, the clinical manifestations usually occur much later in life. Hence the disease has a long symptom-free clinical course. The atherosclerotic process is known to increase with increasing age and to accelerate with and be dependent upon lifestyle as well as upon genetic predisposition (Naghavi et al. 2003a, b).

In order to visualize the atherosclerotic changes, angiographic examinations of the coronary arteries with X-ray opaque dye are frequently conducted. Although these are clinically useful and highly informative diagnostic procedures, they may be difficult to interpret and subject to great variations. A normal coronary angiogram is no guarantee for healthy vessel walls (Naghavi et al. 2003a, b).

Some changes in the vessel wall would not be defined as stenotic changes, because they do not cause a readily detected narrowing of the vessel lumen. Such changes may also have the potential to rupture, and be the cause of a rapidly developed clot that can obstruct the blood flow.

Atherosclerotic processes in turn may lead to a variety of clinical manifestations:

- Acute coronary syndrome (acute myocardial infarction or unstable angina pectoris)
- Stable angina pectoris
- Heart failure
- Sudden cardiac death with cardiac ventricular arrhythmia
- Stroke
- Peripheral artery disease (window-watching disease)

Prevalence of CVD

One of the most conspicuous characteristics of the CVDs is their great variation in prevalence over time and over geographical site. In most Westernized countries, CVD mortality and incidence rates are decreasing. In Sweden, male and female

CVD mortality rates have been cut to less than half of their peak rates, seen in the early 1980s. Incidence rates have not been decreasing as steeply. In contrast, in the developing world, with increasing urbanization and unhealthy changes of lifestyle, CVD rates are increasing and this is a truly global problem.

Several factors have contributed to the substantial change in mortality rates in westernized countries. These factors are concerned with both improved clinical care in the acute phase of a myocardial infarction (monitoring and treatment of life-threatening cardiac arrhythmia) and with better and more efficient efforts to bring down the risk factor levels. Thus both primary and secondary preventive measures have been successful. Even so, improvement in risk factors has been demonstrated to be more important than changes in medical management. The final goal of CVD prevention is in fact to reduce morbidity and mortality in the population, so that ever more people live a longer life with better health-related quality of life.

Scientific evidence is now present that improving and changing habits to a healthier lifestyle will prevent or at least postpone the disease process. This is true for both people who have clinical signs of the disease and those who are still healthy. In the past, preventative measures have been strongly focusing on one single risk factor, such as hypertension, hyperlipidemia, or diabetes. Today we know that the CVD etiology is multifactorial and that risk factors affect each other—positively and negatively (Yusuf et al. 2004).

Women have an overall lower risk of CVD than men. In particular in the younger ages, below age 65, men have twice the risk of women to get a stroke and four times the risk of women (Rosengren et al. 2003) to have a myocardial infarction. In older ages these differences are reduced but never totally subside. Over the age of 80, men still have a higher risk of myocardial infarction. In the end, however, about as many men as women, die from CVD. On average, women have their heart attacks about 5–10 years later in their lives than men.

Heredity and family history of CVD are important characteristics. To describe the family experience of CVD is an important part of the medical history of each CVD patient. Particularly important is the information about genetically determined serious, familial dyslipidemia, which requires specialist management. However, the genetic influence on CVD risk is relatively minor and usually there are other lifestyle-related risk factors as well so that the single effect of genetics is not considerable. Usually the CVD case is due to the fact that other risk factors are present along with a positive family history.

There is now convincing scientific evidence that smoking, nutrition, lack of physical activity, and psychosocial factors are the main causal factors behind CVD. This has become clear from several recent studies, such as the INTERHEART, a multi-center case-control study of 15,000 CVD patients and a similar number of controls from 52 countries all over the world. More than 90 % of the cases could be “explained” by nine risk factors: smoking, lipids, blood pressure, diabetes, central obesity, stress, lack of physical activity, poor nutrition, and alcohol. In this very large study very few people were entirely free from risk factors. The results provide strong evidence for the standard, but also the psychosocial risk factors (Yusuf et al. 2004).

Stress and Psychosocial Factors

In the eyes of the public, psychological stress is linked to myocardial infarction and to stroke, but until fairly recently the evidence for this link has been missing. Today there is compelling evidence and wide knowledge about stress and other psychosocial factors in relation to CVD. In comparison to other standard risk factors, the psychosocial factors are more difficult to define and to assess objectively. In spite of these difficulties there are now several psychosocial dimensions, which are known to influence coronary risk.

Stress at work and in family, negative life events, lack of control, deficient social networks, low socio-economic status (SES), and depression are some of the factors known to influence risk or prognosis in CVD.

Most studies of stress have been focused on the work site. There are a number of studies showing that work stress increases the risk of CVD. The results are not entirely consistent, however. The work stress may partly be due to the social gradients in CVD. SES has long been known as an established risk factor for CVD and work stress often goes with low SES.

There are now also studies that show that stress from family life may also increase the risk and worsen prognosis in CVD, in particular in women. In one study of Stockholm women problems in the spouse relationship, “marital stress,” worsened prognosis more strongly than did the stress from work (Orth-Gomer et al. 2000). In the INTERHEART study, in 15,000 patients, who were compared to an equal number of controls, stress both at work and in the family was clearly more common among CVD patients. It was also shown that a surprisingly large part of underlying risk factors could be ascribed to psychosocial factors (Rosengren et al. 2004).

There is now compelling evidence that stress and other psychosocial risk factors do increase the risk of CVD. Exactly which mechanisms are operating is however still unclear. Experimental animal studies (macaque monkeys) have demonstrated atherosclerosis and endothelial dysfunction in connection with social stress.

Many studies have also linked psychosocial factors to vessel wall dysfunction, to inflammation, to coagulation, and to fibrinolysis.

References

- McGill, H. C., Jr., McMahan, C. A., Zieske, A. W., Tracy, R. E., Malcom, G. T., Herderick, E. E., & Strong, J. P. (2000). Association of coronary heart disease risk factors with microscopic qualities of coronary atherosclerosis in youth. *Circulation*, 102(4), 374–379.
- Naghavi, M., Libby, P., Falk, E., Casscells, S. W., Litovsky, S., Rumberger, J., . . . , Willerson, J. T. (2003a). From vulnerable plaque to vulnerable patient: A call for new definitions and risk assessment strategies: Part I. *Circulation*, 108(14), 1664–1672. Review.
- Naghavi, M., Libby, P., Falk, E., Casscells, S. W., Litovsky, S., Rumberger, J., . . . , Willerson, J. T. (2003b). From vulnerable plaque to vulnerable patient: A call for new definitions and risk assessment strategies: Part II. *Circulation*, 108(15), 1772–1778. Review.

- Orth-Gomer, K., Wamala, S. P., Horsten, M., Schenck-Gustafsson, K., Schneiderman, N., & Mittleman, M. A. (2000). Marital stress worsens prognosis in women with coronary heart disease: The Stockholm Female Coronary Risk Study. *JAMA*, *284*, 3008–3014.
- Rosengren, A., Hawken, S., Ounpuu, S., Sliwa, K., Zubaid, M., & Almahmeed, W. A. (2004). Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): Case-control study. *Lancet*, *364*, 953–962.
- Rosengren, A., Thelle, D. S., Koster, M., & Rosen, M. (2003). Changing sex ratio in acute coronary heart disease: Data from Swedish national registers 1984–99. *Journal of Internal Medicine*, *253*(3), 301–310.
- Yusuf, S., Hawken, S., Ounpuu, S., Dans, T., Avezum, A., Lanas, F., ..., INTERHEART Study Investigators. (2004). Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. *Lancet*, *364*(9438), 937–952.

Chapter 3

Coronary Heart Disease in Women: Evolution of Our Knowledge

Nanette Kass Wenger

Abstract Cardiovascular disease is the leading cause of mortality for women worldwide, in both industrialized countries and developing economies. Despite the dramatic decrease in coronary and cardiovascular mortality for US women each year since 2000, cardiovascular disease remains the leading cause of death for women in the USA. Improvements in coronary outcomes for women likely will be achieved by increasing the inclusion of women in clinical research studies; delineating the biologic mechanism(s) for ischemic heart disease in women, with emphasis on microvascular disease; and increasing awareness of coronary risk by women and their healthcare providers. Requisite is the application of evidence-based data to guide prevention, recognition, and management strategies for women with CHD; as well as exploration of psychosocial/environmental/sociocultural disciplines, their relationship to coronary disease, and their differential impact by gender. Women's cardiovascular health is not solely a medical issue, but also involves public policy; economic, business, ethical, legal, and regulatory issues; community aspects (global, regional, local); and faith-based and cultural associations and interrelationships.

Keywords Coronary heart disease • Women • Coronary risk factors in women • Microvascular angina • Revascularization in women

Introduction/Epidemiology

Despite the dramatic decrease in annual coronary heart disease (CHD) mortality and total cardiovascular mortality for US women each year since 2000, CHD remains the leading cause of death for women in the USA. Cardiovascular disease deaths annually in US women exceed those from all cancers, Alzheimer's disease, chronic respiratory disease, and accidents combined (Roger et al. 2011). Since 1984, more women than men have died each year from CHD (Go et al. 2013). About half of the decline in mortality for women is attributable to more appropriate

N.K. Wenger, M.D., M.A.C.C., M.A.C.P., F.A.H.A. (✉)
Department of Medicine, Division of Cardiology, Emory University School
of Medicine, Atlanta, GA, USA
e-mail: nwenger@emory.edu

and intensive therapies for established and acute coronary illness, with the other half related to coronary risk reduction by primary and secondary preventive strategies. Although women continue to remain underrepresented in clinical trials of cardiovascular therapies (Committee on Women's Health 2013), the results of landmark clinical trials that included women unquestionably have contributed to the improvement in coronary care for women.

Within the USA, considerable health disparities exist among racial and ethnic groups of women, with African American women having the highest prevalence and mortality risk from cardiovascular disease.

Of ominous significance is that in young women, those aged 35–54 years, there has been an increase in coronary mortality annually since 1997, likely attributable to the increased rates of obesity, sedentary lifestyle, diabetes, and dyslipidemia (Ford et al. 2007).

Cardiovascular disease also remains the leading cause of mortality for women worldwide, both in industrialized and in developing economies. It is estimated that by 2040 more women than men will incur cardiovascular death globally (Gholizadeh and Davidson 2008).

Awareness and Education

Campaigns in the USA during the past decade by the National Heart, Lung, and Blood Institute (the Heart Truth Campaign) and the American Heart Association (the Red Dress Campaign) have almost doubled the awareness among US women that cardiovascular disease is their leading cause of mortality. The 30 % awareness rate in 1997 increased to 54 % by 2009 (Mosca et al. 2010), but has since remained unchanged. Unfortunately, awareness is lowest for the subsets of women at highest risk, African American and Hispanic women.

Nonetheless, physician assessment of a woman's cardiovascular risk is characteristically lower than for her male counterparts, which is reflected in the provision of a lesser intensity and quality of cardiovascular preventive therapies for women.

Pathophysiology

Although obstructive coronary artery disease remains the leading cause of myocardial ischemia in women, complex pathophysiologic mechanisms likely play an important role in myocardial ischemia, myocardial infarction, and ischemic heart disease-related mortality for women. In the Women's Ischemia Syndrome Evaluation (WISE) study (Von Mering 2000), microvascular disease was considered an important contributor to myocardial ischemia. About half of all women who present with an acute coronary syndrome do not have significant obstructive disease in their epicardial coronary arteries at angiography.

As well, women appear far more likely to have coronary plaque erosion and thrombosis than men, with less plaque rupture compared to men except at elderly age (Anderson et al. 2000). Abnormalities in coronary vasoreactivity appear to contribute to myocardial ischemia in women with nonobstructive coronary disease (Shaw et al. 2009).

Although women have higher rates of myocardial ischemia and ischemic mortality than men, paradoxical is its association with less obstructive disease in the epicardial coronary arteries and more common preservation of left ventricular systolic function. Better understanding of the pathophysiologic mechanisms of myocardial ischemia in women is requisite to guide improved management.

Coronary Risk Factors, Risk Assessment, and Preventive Strategies

Despite the fact that women and men share the traditional coronary risk factors, these factors impart differential risk by gender. Women smokers have a 25 % greater risk of myocardial infarction than do men who smoke, and smoking is related to almost half of all coronary events in women (Prescott et al. 1998; Huxley and Woodward 2011). The decrease in smoking behavior in the USA has been more prominent for men than for women, with new-onset smoking most common among teenage girls.

Lipid abnormalities also exert a differential risk, with the ratio of total cholesterol: HDL >3.2 highly predictive of cardiovascular events in women, and an HDL-C level <30 mg/dL associated with excess cardiovascular mortality. As well, the combination of increased triglycerides and low HDL imparts increased risk, although no interventions to alter triglyceride or HDL levels have been shown to improve outcomes. The new ACC/AHA guidelines for managing elevated cholesterol levels (<http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437738.63853.7a.citation>) do not have gender-specific recommendations, thus emphasizing the benefits for women of appropriate intensity statin therapy for both primary and secondary prevention. Lipid-lowering therapy, primarily involving statin drugs to reduce LDL cholesterol levels, has dramatically decreased recurrent cardiovascular events in women and likely decreased incident events as well (Ridker et al. 2008; Kaul et al. 2010). A family history of premature CHD also seems more predictive for women than for men (Gulati et al. 2009).

Unique to women is the risk of hypertensive complications of pregnancy: pregnancy-induced hypertension, preeclampsia, and eclampsia. Pregnancy is probably the first “stress test” a woman incurs, and hypertensive complications predict subsequent increased cardiovascular risks (Mosca et al. 2011). Other pregnancy complications predictive of a woman’s adverse future cardiovascular health include gestational diabetes mellitus, preterm birth, fetal growth restriction, and pregnancy loss (Bonamy and Parikh 2013; Wenger 2014b). As well, women with systemic autoimmune collagen vascular disease have an increased cardiovascular risk, warranting coronary risk factor screening for these women.