HEALTH AND AGEING IN OLDER ADULTS:

A gender-specific and life-course perspective

Loes Jaspers

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Gezondheid en veroudering bij mensen van middelbare en oudere leeftijd:
Een genderspecifiek en levensloop perspectief

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op gezag van de
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Chapter 3

Loes Jaspers, Josje D Schoufour, Nicole S Erler, Sirwan K Darweesh, Marileen L Portegies, Sanaz Sedaghat, Lies Lahousse, Bruno H Stricker, Henning Tiemeier, M Arfan Ikram, Albert Hofman, Joop SE Laven, Oscar H Franco*, Maryam Kavousi*. Development of a healthy ageing score in the population-based Rotterdam Study: evaluating age and gender differences. *Journal of the American Medical Directors Association. 2016; in press.*

The association between healthy ageing score with predicted transcriptomic age, predicted DNA methylation age, and with leucocyte telomere length: the Rotterdam Study. *Preliminary draft.*

Loes Jaspers, Nicole S Erler, Bart CJM Fauser, Joop SE Laven, Oscar H Franco*, Maryam Kavousi*. Towards a life-course approach in women's healthy ageing: fertile lifespan characteristics are associated with a healthy ageing score in postmenopausal women of the Rotterdam Study. *Submitted for publication.*

Loes Jaspers, Klodian Dhana, Taulant Muka, Cindy Meun, Jessica C Kiefte-de Jong, Albert Hofman, Joop SE Laven, Oscar H Franco, Maryam Kavousi. Sex steroids, sex hormone-binding globulin and cardiovascular health in men and postmenopausal women: the Rotterdam Study. *Journal of Clinical Endocrinology and Metabolism. 2016; 101(7): 2844-52.*

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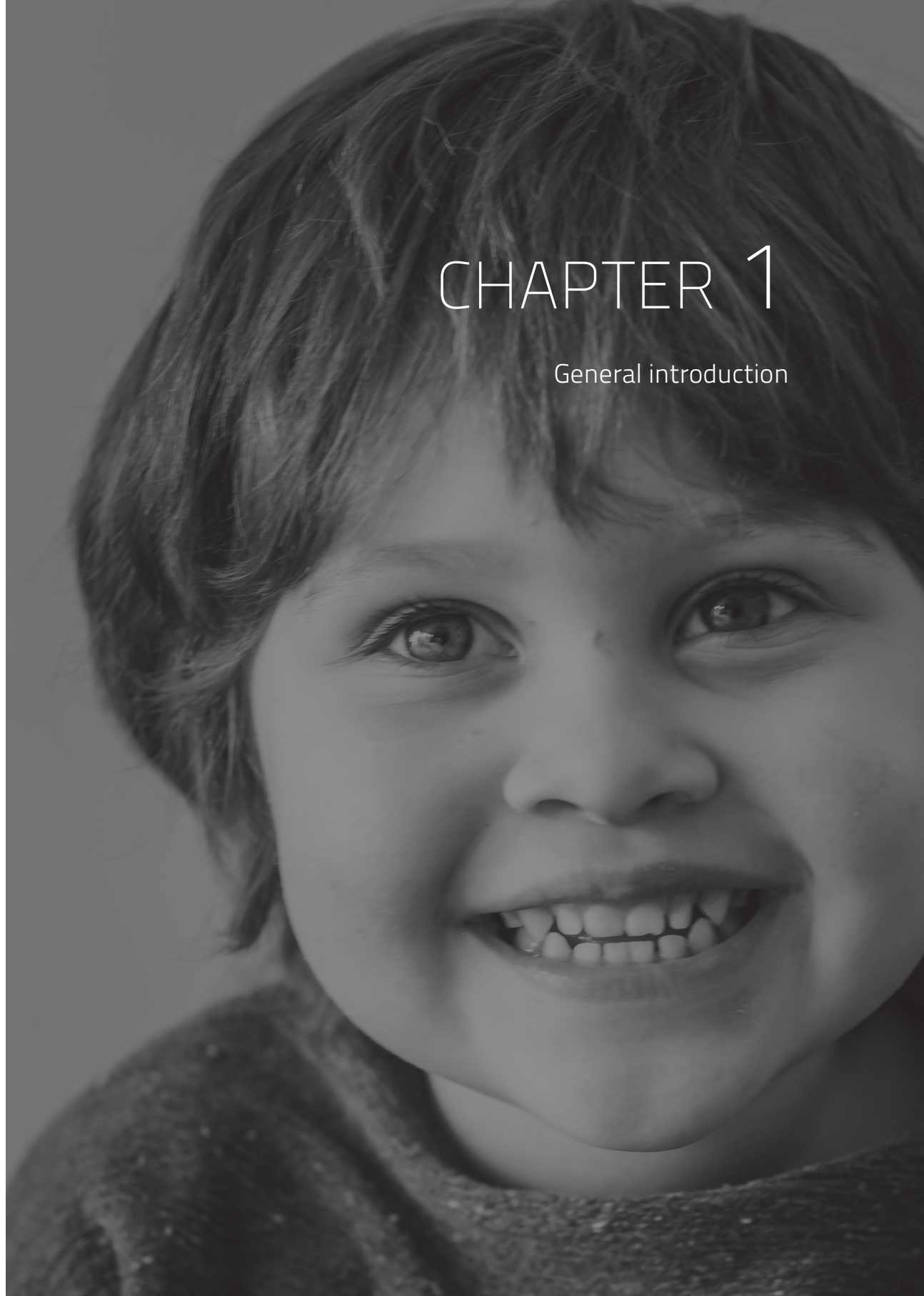
*these authors should be considered similar in author order.

CHAPTER 1

General introduction



Background

Global ageing

Our population is ageing.[1-3] Over the next 30 years, the number of people aged 65 years and older is expected to double from 506 million (7% of the world's population) to 1.3 billion people (14% of the world's population).[4] During the same time period the number of older adults aged 80 years and over (i.e. the oldest old) is projected to increase by 233%.4 By 2050, 80% of older adults will be living in low- and middle income countries.[5] Improvements in healthcare, hygiene and sanitation, and better living standards, in combination with declining fertility rates, are perhaps the main factors behind the observed trend of population ageing.[6]

While people are living longer in all parts of the world, evidence suggests that these years are spent in poorer health.[7] [8] Over the past decades, the main causes of death have transitioned from infectious to age-related non-communicable diseases (NCDs), a phenomenon which is also referred to as the epidemiologic transition.[9] Ischemic heart disease, stroke, and diabetes are among the leading causes of premature death today.[1] Disability-adjusted life years (DALYs) are a widely used measure reflecting the combined burden of years of life lost due to premature mortality and years lived with disability. The total number of DALYs due to NCDs increased from 1.1 billion to 1.5 billion globally between 1990 and 2015, whereas the burden of infectious diseases decreased over time.[10] In 2015, the total DALY burden of NCDs increased mostly because of a rise in cardiovascular diseases, cancer, and mental disorders, among other causes.[10] The burden of NCDs extends beyond morbidity and mortality as it exerts a growing impact on health systems, development, and economic circumstances at all levels of society.[11-15]

What is ageing?

Though ageing and the development of disease can coincide, one should understand that they are not inseparably linked. Ageing is not a disease, though it is often perceived as such.[16] Ageing is a multifactorial process characterized by the progressive loss of physiological integrity and decreasing fertility with advancing age, which could lead to impaired function and increased vulnerability to death.[17] Therefore, ageing research and the study of disease and disability can go hand in hand but could also be viewed as two separate fields of work.

The pursuit of health

The ultimate goal of health care and health systems is to provide people the opportunity to spend their lives in good health. However, past and current health research have focused mainly on risk factors, diseases, and mortality, and only marginally on health or protective factors. This approach may limit our overall understanding of health and the factors that are associated with obtaining, maintaining, and improving health. Particularly in the elderly, the study of disease and disability only minimally reflects the impact it may have on older adult's lives.[18] For example, self-perceived health can differ substantially

from what is measured objectively in the sense that even the diseased and disabled can report high levels of quality of life.[19] [20] Furthermore, multimorbidity (suffering from more than 1 chronic disease at the same time) can have an unfavourable synergistic impact on a person's capacity than you would expect from the summed effect of each separate condition.[21] A better understanding of healthy ageing is becoming increasingly meaningful and has the potential to enhance the lives of individuals and to facilitate the development of adequate strategies with regard to the economic and social implications of ageing populations.[22] So how should we define health?

Definitions of health and its operationalization

The best known definition of health was formulated by the World Health Organization (WHO) in 1948: "a state of complete physical, mental, and social well-being and not

Table 1. Definitions of health and healthy ageing.

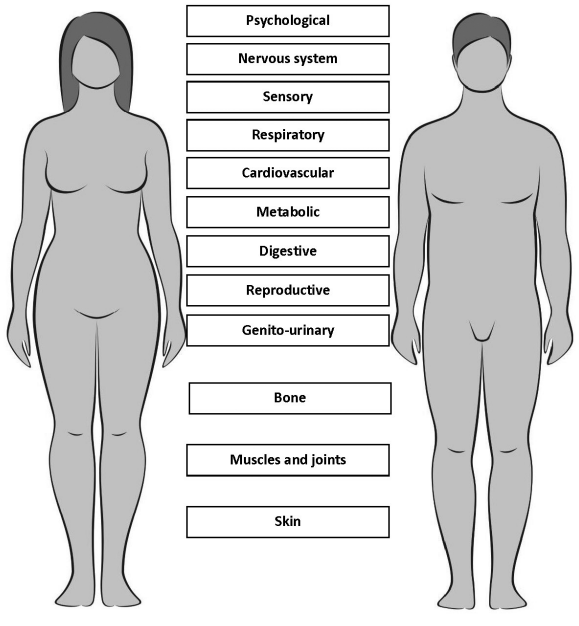
Definitions of health	
Huber et al, 2011[23]	"Health is the ability to adapt and to self-manage in the face of social, physical, and emotional challenges."
Bircher, 2005[24]	"Health is a dynamic state of wellbeing, characterized by a physical, mental, and social potential, which satisfies the demands of life commensurate with age, culture, and personal responsibility. If the potential is insufficient to satisfy these demands the state is disease."
Spencer, 19th century	"Health is the perfect adjustment of an organism to its environment."
Definitions of healthy ageing	
WHO report on ageing and health, 2015[25]	"Healthy ageing is the process of developing and maintaining the functional ability that enables well-being in older age."
Franco et al, 2009[26]	The Healthy Ageing Phenotype (HAP) can be defined as the condition of being alive, while having highly preserved functioning metabolic, hormonal, and neuro-endocrine control systems at the organ, tissue and molecular levels." It is further characterized by a higher degree of physiological complexity which translates into optimal reserves and biological resilience to respond to and accommodate daily stressors.
Rowe and Kahn, 1997[27]	"Successful ageing can be defined as the combination of a low probability of disease and disease-related disability, high cognitive and physical functional capacity, and active engagement with life."

merely the absence of disease and infirmity".[28] Over time, this definition has become unproductive for several reasons. The static nature of the definition is challenged by the shift from acute to chronic diseases, making an increasing number of chronically diseased permanently ill. Furthermore, although "complete well-being" is a desirable goal, it is both hard to achieve and challenging to operationalize. More recent definitions of health and healthy ageing have been influenced by the work of sociologist Aaron Antonovsky. His theory of salutogenenis (as opposed to pathogenesis) rejects the sharp distinction between health and disease and positions individuals along the "health-ease dis-ease continuum".[29] The flexibility in this way of thinking resonates in contemporary definitions of both health and healthy ageing today (*Table 1*).

Within definitions of health, different body systems could be considered subdomains of health, such as cardiovascular health or sexual health (*Figure 1*). The complex physiological mechanisms within these subdomains, which can interact with both psychological as well as social functioning, can differ between men and women and across stages of life.

Currently, several definitions for healthy ageing have been formulated and operationalized in populations.[25-27 30-34] However, to date, measurement of healthy ageing is not performed in a standardized manner. It has been suggested that healthy ageing measurement tools should include assessment of mental health and self-perceived health on top of the

Figure 1. Key health domains in men and women.



overrepresented physiological measures,[35-37] and that continuum-based tools for healthy ageing might better capture the heterogeneity of the phenotype, as opposed to the more widely adopted dichotomous approaches.[36 38] An example of an effort to operationalize health measurement is the concept of cardiovascular health, which was introduced by the American Heart Association in 2010.[39] The concept of cardiovascular health includes ideal levels of 7 metrics, 3 of which are health factors (total cholesterol, fasting glucose, and blood pressure) and 4 of which are health behaviours (physical activity at goal, non-smoking, normal body mass index, and a healthy diet).[39] Cardiovascular health has been related to different risk factors and diseases of the cardiovascular system and beyond.[40-50] There is a paucity of research that effectively translates definitions of health into manageable measures, which could be applied to individuals and populations. Although the appreciation of a health-focused approach is increasingly gaining attention, it remains to be elucidated how the concepts of health apply to men and women, populations, and across stages of life and how health measurement should be operationalized.

A gender-specific perspective

Worldwide, men are outlived by women by 6 to 8 years. However, women generally spend these additional years with more disease and disability: 'men die quicker, women get sicker'. This is also referred to as the 'male-female disability-survival paradox', which describes that women's longer lives are not necessarily healthy lives.[51-53] To date, it is not well understood which mechanisms underlie the male-female disability-survival paradox. It could be possible that sex-specific gene expression and differential effect of sex hormones in men and women underlie this paradox.[54] Furthermore, men and women differ with regard to their symptom perception and attribution, patient delay for consulting health professionals, and over reporting of worse health outcomes in women.[55-57] Also, less pathognomonic symptom presentation in women may lead to diagnostic delays and less timely treatment initiation, which could result in more severe consequences in terms of long-term disability.[54] It may also be possible that men have greater severity of disease, resulting in higher mortality.[57] In summary, the observed differences between men and women may be explained by the interaction between social, psychological, behavioural, and biological factors.

Although there is enough evidence that men and women are different, by default studies still combine men and women in their analyses. Historically, women were even excluded from study to prevent biases due to hormonal differences between men and women. Moreover, former trials assessing the benefits and harms of medical treatments predominantly included men. To some extent this still happens today. For example, in the safety evaluations for the approval of flibanserin as a medical treatment for women with hypoactive sexual desire disorder, the interaction between flibanserin and alcohol was evaluated in 25 persons, of which 23 were men.[58] Combining men and women in research analyses or extrapolating findings in men to women can result in delayed or wrong diagnoses, more severe burden of disease, and wrong treatment choices, particularly in women.[59] Consequently, this can lead to increased health care spending and preventable

mortality.[59] Therefore, gender-specific research is needed to adequately support health systems to facilitate health for men and women equally.

A life-course approach in women's health

Another explanation for the differences in health observed between men and women is embedded in the different reproductive challenges and opportunities that men and women encounter earlier in life.[3 60 61] There is growing support that functioning, disease, and health in older adults share common pathways with accumulative life experiences, which can start as early as in utero.[62 63] Specifically in women, timing of menarche and menopause, and number and timing of pregnancies, can greatly affect postmenopausal health.[64 65] In addition, ovarian function and the decline of ovarian function over time exerts effects on long-term health in women that extend beyond the reproductive domain. Thus, it has been suggested that reproductive performance in women constitutes a good predictor for general health in later life.[66] Furthermore, women today spend almost half of their lives in postmenopause. Menopause is defined as the permanent loss of ovarian function.[66 67] The onset of menopause is preceded by the menopausal transition, a period during which substantial short and long term alterations in different domains occur. The importance of a life-course approach in women's health has only recently been adopted in guidelines for women's health,[68 69] but studies are still scarce. To what extent earlier life experiences, such as reproductive performance, and the menopausal transition impact menopausal health remains to be elucidated.[70]

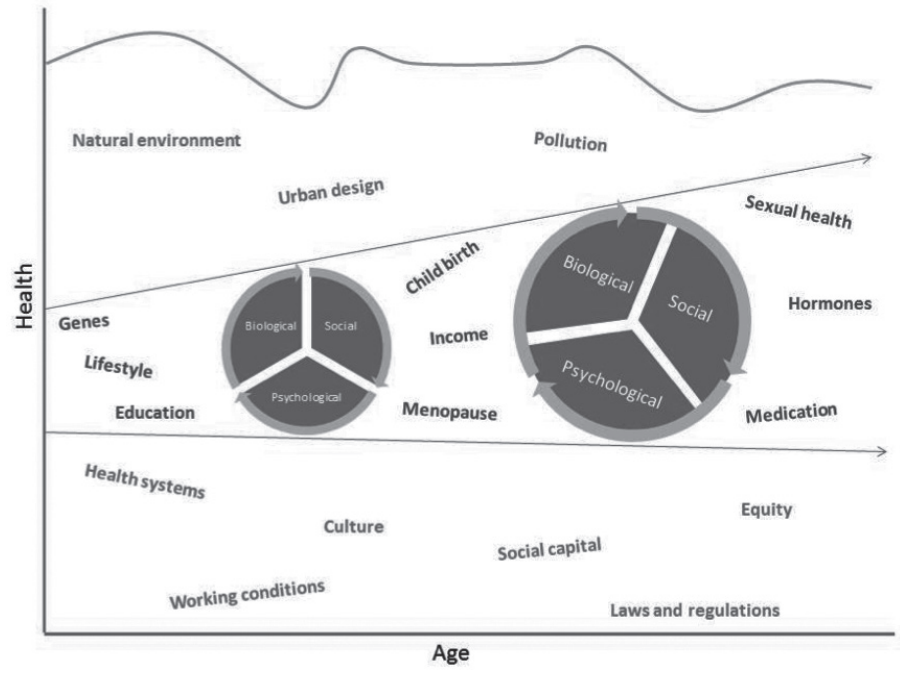
Conceptual framework and aims of this thesis

In our contemporary societies, where we have the prospect of living over 100 years, it is becoming increasingly urgent to study health in our ageing populations using a gender-specific and life-course perspective. The conceptual framework of this thesis is presented in *Figure 2*. The y-axis of the figure represents health and the x-axis represents age. The two circles reflect the combination of the biological, psychological, and social functioning which can change while ageing. The area within the two lines contains characteristics that belong to an individual or to a population, and can affect healthy ageing. These include, among others, fertility, menopause, medication use, lifestyle, sex hormones, or subdomains of health such as cardiovascular health and sexual health. The area outside of the lines encompasses characteristics which can affect healthy ageing that lie beyond the individual or population. Such characteristics include the natural environment, the health system, working conditions, culture, and more. The combination of these aspects of health and ageing are integrated into the fluctuating line at the top of the figure. This represents healthy ageing as a dynamic state, which is shaped by biopsychosocial functioning and is affected by characteristics that belong to the individual or population and beyond.

A better understanding of the patterns and determinants of health has the potential of promoting and sustaining health in men and women. Moreover, improvements in measuring and monitoring health can contribute to a better aligning of health systems with the needs of ageing populations and could facilitate the development of age-friendly environments.

In this thesis, we aim to provide insights into health and ageing whilst adopting an integrated, gender-specific, and life-course approach. As a first step in this thesis we have explored how big the economic impact of NCDs was on households and impoverishment and on health care costs as well as in terms of national income. Thereafter, following the pursuit of health, we have developed a healthy ageing score. We have also applied the new concept of cardiovascular health to the population-based Rotterdam Study and investigated further gender differences and the role of sex steroids. Furthermore, in women, we have specifically focused on conceptualizing healthy menopause and on the role of reproductive experience which occurred between menarche and menopause and different types of ovarian dysfunction, in cardiometabolic and overall health.

Figure 2. Conceptual framework of this thesis.



The two arrows reflect health trajectories within an individual or population. The circles represent the interaction between biological, psychological, and social domains of health, which can differ across stages of life. The words in the figure are factors within individuals, populations or in the environment that can affect healthy ageing. All of the above are summarized in the fluctuating line at the top of the figure, which represents healthy ageing as a dynamic state, which can fluctuate over time.

General outline of this thesis

Subsequent to this general introduction, the aims of this thesis will be addressed in several chapters. In the second chapter, we have studied the economic impact of NCDs by performing two systematic reviews. The first systematic review is presented in **Chapter 2.1**, and focuses on the micro-economic impact of NCDs on households and impoverishment. The second systematic review is presented in **Chapter 2.2**, and zooms in on the macro-economic impact of NCDs on health care spending and national income.

In **Chapter 3** we present the results of the studies on the healthy ageing score and cardiovascular health in the population-based Rotterdam Study. In **Chapter 3.1** we describe the development of a healthy ageing score and evaluate age and gender differences. In **Chapter 3.2** we explore to what extent the healthy ageing score impacts biological markers of ageing, including telomere length and transcriptomic ageing. While adopting a life-course approach in **Chapter 3.3**, we assess the association between women's fertile lifespan characteristics and sex steroids with the healthy ageing score in postmenopausal women. **Chapter 3.4** describes the relation between sex steroids with cardiovascular health and denotes differences herein between men and women.

In **Chapter 4** we focus more specifically on women's sexual, reproductive, and menopausal health. In **Chapter 4.1** we present a conceptual framework for healthy menopause. In **Chapter 4.2** we study androgen levels in women with various forms of ovarian dysfunction and the association between androgens and cardiometabolic factors. **Chapter 4.3** describes the relation between women's fertile lifespan characteristics with all-cause and cause-specific mortality in postmenopausal women. **Chapter 4.4** comprehensively summarizes the efficacy and safety of flibanserin for women with hypoactive sexual desire disorder, by means of a systematic review and meta-analysis.

Finally, in the general discussion (**Chapter 5**) we summarize the principal findings of this thesis and discuss the main methodological considerations. We reflect on the findings and implications from different perspectives, the population, clinical, and policy perspective and conclude with several directions for future research.

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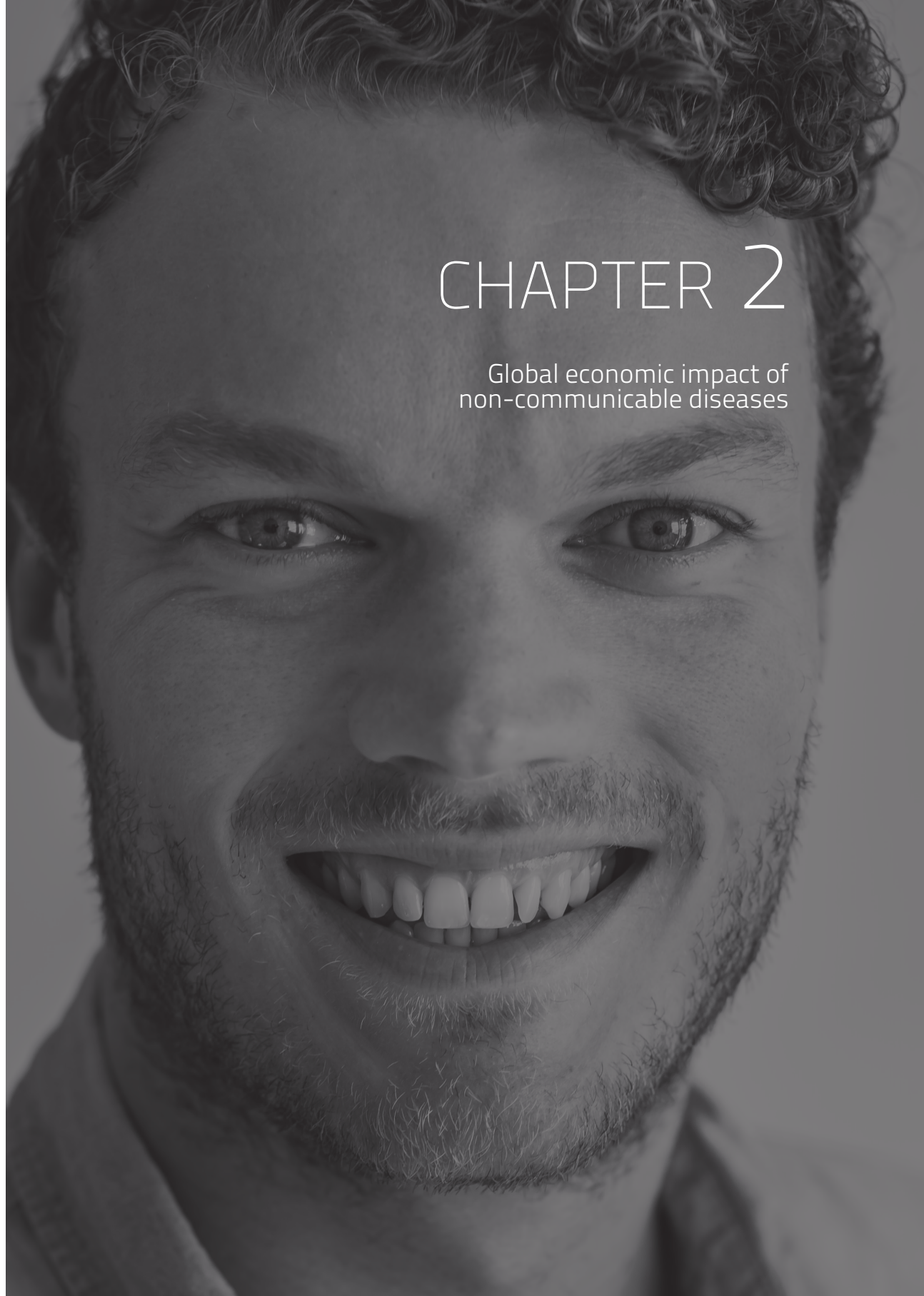
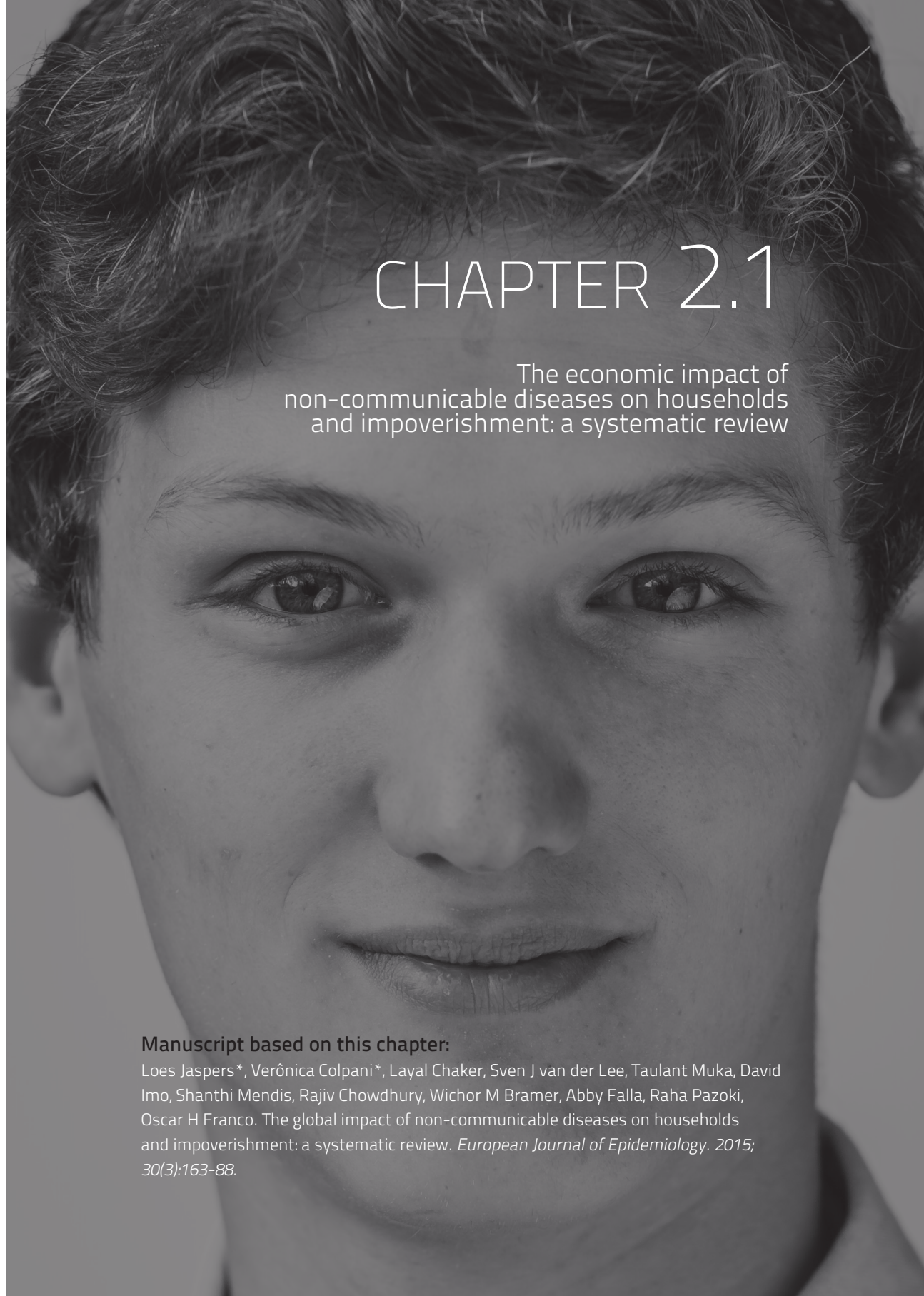


CHAPTER 2

Global economic impact of non-communicable diseases



CHAPTER 2.1

The economic impact of non-communicable diseases on households and impoverishment: a systematic review

Manuscript based on this chapter:

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ABSTRACT

Background:

The global economic impact of non-communicable diseases (NCDs) on household expenditures and poverty indicators remains less well understood.

Objective:

To conduct a systematic review and meta-analysis of the literature evaluating the global economic impact of six NCDs (including coronary heart disease, stroke, type 2 diabetes mellitus (DM), cancer (lung, colon, cervical and breast), chronic obstructive pulmonary disease (COPD) and chronic kidney disease (CKD)) on households and impoverishment.

Data sources:

Medline, Embase and Google Scholar databases were searched from inception to November 6th 2014. To identify additional publications, reference lists of retrieved studies were searched.

Study selection:

Randomized controlled trials, systematic reviews, cohorts, case-control, cross-sectional, modeling and ecological studies carried out in adults and assessing the economic consequences of NCDs on households and impoverishment. No language restrictions. All abstract and full text selection was done by two independent reviewers.

Data extraction:

Data were extracted by two independent reviewers and checked by a third independent reviewer.

Main outcome measures:

Studies were included evaluating the impact of at least one of the selected NCDs and on at least one of the following measures: expenditure on medication, transport, co-morbidities, out-of-pocket (OOP) payments or other indirect costs; impoverishment, poverty line and catastrophic spending; household or individual financial cost.

Results:

From 3241 references, 64 studies met the inclusion criteria, 75% of which originated from the Americas and Western Pacific WHO region. Breast cancer and DM were the most studied NCDs (42 in total); CKD and COPD were the least represented (five and three studies respectively). OOP payments and financial catastrophe, mostly defined as OOP exceeding a certain proportion of household income, were the most studied outcomes. OOP expenditure as a proportion of family income, ranged between 2-158% across the different NCDs and countries. Financial catastrophe due to the selected NCDs was seen in all countries and at all income levels, and occurred in 6-84% of the households depending on the chosen catastrophe threshold. In 16 low- and middle-income countries (LMIC), 6-11% of the total population would be impoverished at a 1.25 US dollar/day poverty line if they would have to purchase lowest price generic diabetes medication.

Conclusions:

NCDs impose a large and growing global impact on households and impoverishment, in all continents and levels of income. The true extent, however, remains difficult to determine due to the heterogeneity across existing studies in terms of populations studied, outcomes reported and measures employed. The impact that NCDs exert on households and impoverishment is likely to be underestimated since important economic domains, such as coping strategies and the inclusion of marginalized and vulnerable people who do not seek health care due to financial reasons, are overlooked in literature. Given the scarcity of information on specific regions, further research to estimate impact of the separate NCDs on households and impoverishment in LMIC, especially the Middle Eastern, African and Latin American regions is required.

Keywords:

non-communicable diseases, impoverishment, households, systematic review

INTRODUCTION

Improvements in healthcare, hygiene and sanitation have increased the possibility to live until older age. Together with a growing global population, this has meant that non-communicable diseases (NCDs), including coronary heart disease (CHD), stroke, chronic obstructive pulmonary disorder (COPD), cancer, type 2 diabetes mellitus (DM) and chronic kidney disease (CKD), are now the leading causes of morbidity and mortality worldwide. The burden exerted by NCDs extends beyond morbidity and mortality and generates an enormous societal impact, including on households and impoverishment.[1-5]

Limited insurance coverage and lack of social security nets can force households of NCD patients to spend large amounts of money out-of-pocket (OOP). NCDs reduce family income, savings and consumption of non-health items, and prompt early retirement.[6,7] The impact of NCDs on households is likely to be especially severe in low- and middle-income countries (LMIC) where low-income populations, many of whom already experience extreme absolute poverty and precarious living conditions, are especially vulnerable to impoverishment due to any degree of healthcare spending.[1,8-10] With some exceptions, such vulnerable groups suffer a double burden of chronic and infectious diseases.[2,10-13] The interplay between exposure to disease and financial vulnerability among low-income households can drive families and societies into deeper poverty.

Despite greater appreciation on the likely deleterious role of NCDs on households and impoverishment, the extent of this impact in various geographical regions, is unclear. While several studies have addressed the issue, they have not been systematically evaluated in a single comprehensive investigation. Therefore, we report a systematic review to investigate the economic consequences of the major NCDs on the micro-economic indicators (i) at the level of households (such as consumption choices, coping strategies, OOP, direct and indirect costs) and (ii) of poverty (such as financial burden, catastrophic spending, impoverishment, poverty line and financial vulnerability), across various global regions.

METHODS

Conceptual framework

To guide the systematic review of the literature regarding the household impact of NCDs, a conceptual framework was adopted. This theory, previously described by McIntyre and colleagues, focuses on the economic consequences of illness and paying for health care.[14] The economic consequences that NCDs incur on the household level are preceded by levels of perceived illness and the resulting treatment seeking behaviour. Seeking care can lead to economic consequences in the form of direct (e.g. costs for hospitalization, medicines, transportation) and indirect costs (e.g. time costs of informal caregivers, time costs of the ill). The indirect costs associated with not seeking care can exert a similar burden on the microeconomic level. Economic consequences in combination with divergent coping strategies (e.g. household labour substitution, use of savings, changing consumption choices) can result in poverty.

Although the importance of the first two steps (perceived illness and treatment seeking behaviour) is conclusive, the focus of this review was on economic consequences, coping strategies and poverty

Search strategy and inclusion criteria

We conducted a systematic search of electronic medical databases (Medline, Embase and Google Scholar) from inception to November 6th 2014 to identify scientific articles assessing the economic consequences of NCDs on households and on impoverishment. Given their large burden in populations worldwide, the following NCDs were selected: CHD, stroke, COPD, DM, cancers (lung, colon, breast, and cervical) and CKD.1 The step-wise inclusion and exclusion procedure outlined in *Figure 1* was followed. Eligible study designs included randomized controlled trials (RCTs), systematic reviews (used to identify further references), cohort, case-control, cross-sectional, ecological studies and modeling studies. Studies were included evaluating the impact of at least one of the selected NCDs and on at least one of the measures of interest: expenditure on medication, transport, co-morbidities, OOP or other indirect costs; consumption choices, coping strategies, impoverishment, poverty line and catastrophic spending; the household or individual financial cost. Only studies carried out in adults (>18 years old) were included and no language or date restrictions were considered. The search strategy in *Appendix 1* was applied.

Study selection

Two independent reviewers reviewed the abstracts and selected eligible studies. Any disagreements between the two reviewers were resolved through consensus or consultation of a third reviewer. To ensure consistent application of the inclusion criteria, a sample of the full texts was reviewed by a third reviewer. The references of the retrieved studies were scanned to identify additional relevant publications that were missed by the initial search. Authors of included studies were contacted to retrieve missing full texts and to identify any missing studies.

Data extraction

A data collection form was prepared to extract the relevant information from the included full texts, including study design, World Health Organization (WHO) region, characteristics of study participants, and characteristics of the NCDs evaluated and measures included. Local currencies were converted to US dollars (USD) to enhance comparability between the eligible studies, preferably using exchange rates given by the studies, if used. If no exchange rate was given, a conversion rate of the publication year of the study was used. All USD were converted to dollars of 2013 using the consumer price index conversion factors.[15]

Quality evaluation

To evaluate the quality of all studies included, the Newcastle-Ottawa Scale (NOS) was applied.[16] NOS scale assesses the quality of the articles in three domains of selection, comparability and exposure. Within the selection category, four items are assessed and maximum one star can be awarded to each item. Two stars can be awarded to the one item within the comparability category. Finally, one star can be awarded to each of the three items in the exposure category. A score was made by adding up the number of stars and therefore, NOS scale can have maximum nine stars for the highest quality. For cross-sectional and descriptive studies, an adapted version of NOS scale was used (*Appendix 2*).

Statistical analyses

Heterogeneity permitting, we sought to pool the results using a random effects meta-analysis model. If pooled, results were expressed as the pooled estimate and the corresponding 95% confidence intervals. All costs presented are converted in USD 2013.

RESULTS

From 3.241 references initially identified, 64 studies met the inclusion criteria (*Figure 1 and Table 1*).[17-80] The eligible studies were published between 1999 and 2014, and included more than 835 million individuals.

General characteristics of the included studies

Of these 64 studies, three studies focused on multiple WHO regions, 20 studies originated from the WHO Western Pacific region and 25 from the WHO region of the Americas (22 from Canada or the United States of America (USA)). Thirteen studies were from South-East Asia (eight from India); five studies from Europe and the African region contributed four studies. We found three studies from the Eastern Mediterranean region.

Fifty-seven studies had an observational design, of which twelve were prospective cohort studies, one was retrospective and 44 cross-sectional. One study presented a retrospective analysis of a randomized clinical trial and six were economic modelling studies. Most of the studies (51) used solely self-reported NCDs and economic measures data. Eligible participants were mostly sampled from hospitals, from disease registries or the general population. The remaining thirteen studies used data from regional, national and international databases and insurance data. In less than half of the studies, a control group was present; this was either a sample of the general population or sometimes sought within the same environment as the patients (e.g. same insurance company, same registry).

Sixteen studies focused on the impact of more than one NCD on households and impoverishment. The most frequently studied diseases were breast cancer and DM. Of the studies reporting on cancers, breast cancer was included in 21 studies, followed by colon cancer (eleven studies), lung cancer (eight studies) and cervical cancer (four studies). Two studies mentioned cancer, without specifying cancer types. Diabetes mellitus was the NCD of interest in 21 studies, stroke in ten, CVD in eight and CKD in five studies. Three studies focused on COPD and three on NCDs in general terms.

Quality of the included studies

A quality score was appointed to all except 2 of the 64 included studies (*Tables 2A-G*). In these two studies quality assessment was unfeasible due to their methodology and design. The median quality score over all the studies was 4.5 out of 9 (interquartile range 3 to 6). Two thirds of the eligible studies scored 5 points or less, indicating that the majority of the studies were of low or moderate quality.

Figure 1. Flowchart of studies for the global economic impact of NCDs on households and impoverishment.

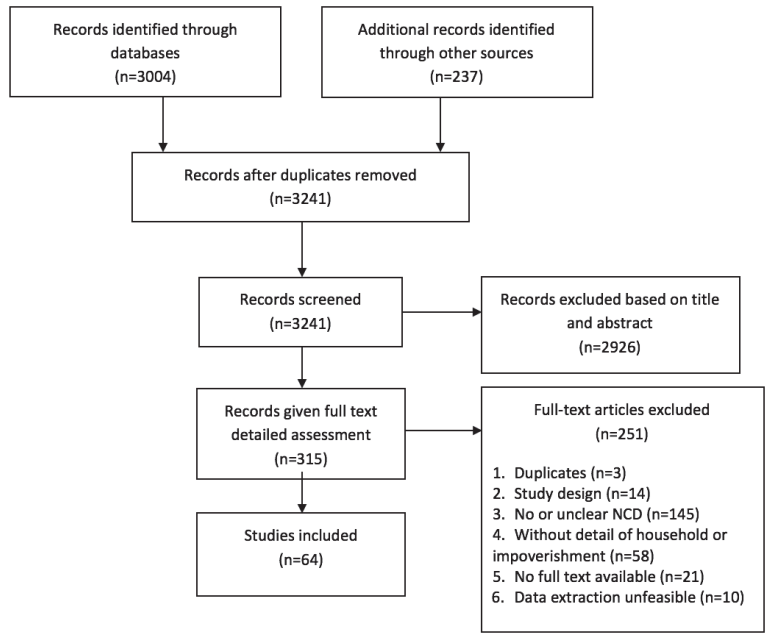

Table 1. General characteristics of the studies included in this review.

Source	Period of surveillance	Location	WHO region	Study design	Number in analysis	Gender	Ethnicity	Reported NCD
Arozullah et al,[72] 2004	1999-2002	USA	Americas	Cross sectional	156	Female	White/Caucasian 26%, Black/African 10%, Latino/Hispanic 5%, Asian 4%, other 1%	Breast cancer
Arrossi et al,[71] 2007	2002-2004	Argentina	Americas	Cross sectional	120	Female	NR	Cervical cancer
Baanders and Heijmans,[70] 2007	2003	Netherlands	Europe	Cross sectional	1093	Both	NR	DM,CVD and
Banthin and Bernard,[69] 2006	1996-2003	USA	Americas	Economic modeling study	47992	Both	NR	DM, CVD, stroke, CKD and cancer
Bennett et al,[68] 2009	2007-2008	New Zealand	WPR	Cross sectional	68	Both	White 88.2%, Maori 7.4%, Pasifica 1.5%, other 2.9%	Breast, colon and cervical cancer
Campbell et al,[67] 2011	2002-2005	USA	Americas	Cross sectional	622401	Both	NR	DM, CKD
Chang,[66] 2010	2006-2007	Taiwan	WPR	Cross sectional	498	Both	NR	DM
Chatterjee et al,[65] 2011	2008	Thailand	SEAR	Cross sectional	190	Both	NR	DM
Chirikos et al,[63] 2002a	NR	USA	Americas	Case control	210	Female	White 90%, Hispanic 4%	Breast cancer
Chirikos et al,[64] 2002b	NR	USA	Americas	Case control	210	Female	White 90%, Hispanic 4%	Breast cancer

Table 1. Continued

Source	Period of surveillance	Location	WHO region	Study design	Number in analysis	Gender	Ethnicity	Reported NCD
Davidoff et al,[62] 2013	1997-2007	USA	Americas	Cohort study	1868	Both	White 82.1%, Black 8.6%. Hispanic 5.8%, other 3.5%	Breast, lung and colon cancer
Dewey et al,[61] 2003	1997	Australia	WPR	Economic modeling study	263	Both	NR	Stroke
Eaker et al,[60] 2011	1993-2003	Sweden	Europe	Cohort study	28566	Female	NR	Breast cancer
Engelgau et al,[59] 2012	1995 - 2004	India	SEAR	Cross sectional	1080000	NR	NR	DM, CVD and cancer
Essue et al,[58] 2011	2001-2008	Australia	WPR	Cross sectional	218	Both	NR	COPD
Essue et al,[57] 2012	NR	Australia	WPR	Prospective cohort study	414	Both	NR	Stroke
Essue et al,[56] 2013	2001-2008	Australia	WPR	Cross sectional	247	Both	NR	CKD
Falconer et al,[55] 2010	NR	Vanuatu	WPR	Cross sectional	172	Both	NR	DM
Gerzeli et al,[54] 2005	NR	Italy	Europe	Economic modeling study	449	Both	NR	Stroke
Goldhaber-Fiebert et al,[53] 2010	2005-2008	India, China, Thailand and Malaysia	SEAR, WPR	Cross sectional	10875	Both	NR	DM
Gordon et al,[52] 2007	2002-2004	Australia	WPR	Longitudinal study	296	Female	NR	Breast cancer

Table 1. Continued

Source	Period of surveillance	Location	WHO region	Study design	Number in analysis	Gender	Ethnicity	Reported NCD
Gordon et al,[51] 2009	2006-2007	Australia	WPR	Cross sectional	139	Female	NR	Breast cancer
Grover et al,[50] 2005	NR	India	SEAR	Cross sectional	50	Both	NR	DM
Heeley et al,[49] 2009	2006	China	WPR	Prospective cohort study	6416	Both	NR	Stroke
Higashiyama et al,[48] 2009	2002-2003	Japan	WPR	Cohort study	4026	Both	NR	CKD
Huffman et al,[47] 2011	NR	Argentina, China, India, Tanzania	Americas, Africa, SEAR, WPR	Cross sectional	1655	Both	NR	CVD
Jeon et al,[46] 2009	2007-2008	Australia	WPR	Cross sectional	66	Both	NR	COPD, DM
Joshi et al,[45] 2013	Feb-April, 2010	India	SEAR	Cross sectional	166	Both	NR	DM
Kang et al,[44] 2011	2001-2004	Korea	WPR	Economic modeling study	50000000a	NR	NR	Stroke
Khowaja et al,[43] 2007	July-Sep 2006	Pakistan	EMR	Cross sectional	345	Both	NR	DM
Lauzier et al,[40] 2008	2003	Canada	Americas	Prospective cohort study	459	Female	NR	Breast cancer
Lauzier et al,[42] 2011	2003	Canada	Americas	Prospective cohort study	693	Female	NR	Breast cancer
Lauzier et al,[41] 2013	2003-2004	Canada	Americas	Prospective cohort study	1191	Both	NR	Breast cancer

Table 1. Continued

Source	Period of surveillance	Location	WHO region	Study design	Number in analysis	Gender	Ethnicity	Reported NCD
Longo and Bereza,[39] 2011	NR	Canada	Americas	Cross sectional	282	Both	NR	Breast, lung and colon cancer
Markman and Luce,[38] 2010	May, 2008	USA	Americas	Cross sectional	1767	Both	NR	Breast, lung and colon cancer
McKevitt et al,[37] 2011	Feb-Jun 2009	UK	Europe	Cross sectional	799	Both	White:90%, Black 6%	Stroke
Moore,[36] 1999	NR	USA	Americas	Cross sectional	30	Female	White 43%, Black 53%, Asian/Pacific 3%	Breast cancer
Niens et al,[35] 2010	2000-2006	16 countries	All except Europe	Economic modeling study	763234000 [a]	NR	NR	DM
Obi and Ozumba,[34] 2008	1995-2004	Nigeria	Africa	Cross sectional	144	Women	NR	Cervical cancer
Okumura and Ito,[33] 2013	2007	Japan	WPR	Cross sectional	20736	Both	NR	DM, CVD and stroke
Pisu et al,[32] 2011	NR	USA	Americas	Retrospective trial analysis	261	Female	Caucasian 82%, Minority 18%	Breast cancer
Ramachandran et al,[31] 2007	1998-2005	India	SEAR	Cross sectional	556	Both	NR	DM
Rao et al,[30] 2011	2004	India	SEAR	Cross sectional	2567	Both	NR	DM and CVD
Rayappa et al,[29] 1999	NR	India	SEAR	Cross sectional	620	Both	NR	DM

Table 1. Continued

Source	Period of surveillance	Location	WHO region	Study design	Number in analysis	Gender	Ethnicity	Reported NCD
Rodbard et al,[28] 2010	2005-2006	USA	Americas	Cross sectional	3551	Both	White 85%	DM
Shankaran et al,[27] 2012	2008-2010	USA	Americas	Cross sectional	555	Both	White 83.5%, nonwhite 16.5%	Colon cancer
Shobhana et al,[26] 2000	NR	India	SEAR	Cross sectional	596	Both	NR	DM
Shugarman et al,[25] 2007	1996-1999	USA	Americas	Cross sectional	6657	Both	White 91.2%, Black 8.8%	Colon cancer
Su et al,[24] 2006	2000-2001	Burkina Faso	Africa	Cross sectional	6192	NR	NR	NCD
Sun et al,[23] 2009	2005-2006	China	WPR	Cross sectional	3944	Both	NR	NCD
Syse and Tonnessen,[22] 2012	2008	Norway	Europe	Economic modeling study	1039100	Both	NR	Breast, cervical, colon and lung cancer
Thuan et al,[21] 2006	2001-2002	Vietnam	WPR	Cross sectional	2727	NR	NR	NCD
van Houtven et al,[20] 2010	2005	USA	Americas	Cross sectional	1629	Both	White 77.8%, Black/African 14.1%, Latino 5.4%, other 13.3%	Colorectal and lung cancer
Yabroff et al,[19] 2008	1999-2003	USA	Americas	Cross sectional	718907	Both	NR	Breast, lung and colorectal cancer
Zaidi et al,[18] 2012	2009-2010	Pakistan	EMR	Cross sectional	67	Female	NR	Breast cancer

Table 1. Continued

Source	Period of surveillance	Location	WHO region	Study design	Number in analysis	Gender	Ethnicity	Reported NCD
Zhou et al,[17] 2008	2005-2006	China	SEAR	Cross sectional	1631	Both	NR	Breast, lung and colorectal cancer

[a] Population numbers based on World Bank Data, http://www.worldbank.org/
COPD=chronic obstructive pulmonary disease, CKD=chronic kidney disease, CVD=cardiovascular disease, DM=diabetes mellitus, EMR= Eastern Mediterranean Region, NCDs=noncommunicable diseases, NR=not reported, SEAR=South-East Asia Region, UK=United Kingdom, USA=United States of America, WHO=World Health Organization, WPR=Western Pacific Region.

Measures of economic impact on households and impoverishment

There was substantial heterogeneity among the studies in the measurement methods of the economic impact of NCDs on households and impoverishment. Therefore, pooling the outcomes of the included studies was not feasible.

For economic consequences (i.e. direct and indirect costs), OOP cost was the most common measure evaluated and was reported either as absolute costs or as a percentage of varying income proxies (e.g. individual income, family income, monthly non-food expenditure or household capacity to pay). Different OOP definitions were applied and could include the following expense types: cost of treatment or hospitalization (direct medical costs) and, among others, costs for transportation, food and lodging (referred to as direct non-medical costs or indirect costs). For catastrophic spending, mostly defined as a scenario in which OOP costs exceed a certain percentage of household income, different thresholds ranging from 10-40% were used. Studies applying higher thresholds (e.g. 40%) did not necessarily find lower percentages of households that experience financial catastrophe when compared to studies using lower thresholds (e.g. 10%). Two other frequently reported measures of micro-economic burden were income loss and perceived financial hardship (e.g. worries about or change for the worse in financial situation), the latter capturing a different, more subjective perspective of the economic impact of NCDs on individuals and households.

Of the 64 eligible studies, five reported on the impact of NCDs on coping strategies, wherein the applied definitions differed between studies. Impoverishment was reported in three studies and was expressed as the percentage of people dropping below the 1, 1.25 or 2 US dollar (USD) per day poverty line due to the economic burden of treatment.

Impact of cardiovascular disease

Huffman et al. (*Table 2A*) reported that 14.3% of high-income families in China experienced some form of household income loss due to cardiovascular disease (CVD) hospitalization, rising to 26.3% in India, to 63.5% in Tanzania, and to 67.5% in Argentina. This impact was patterned by socio-economic position, as greater household CVD-attributable income losses were reported for lower income groups.[47] In the USA, 10.4% of CHD patients reported that OOP spending was more than 20% of the family income.[69] CVD patients in India spent 30% of their annual family income on direct CVD health care, where mean OOP per hospitalization increased from 364 USD in 1995 to 575 USD in 2004.[30 59] In CVD-affected households in India, >30% borrowed or sold assets to pay for inpatient treatment, compared to 12% in matched control households.[78] Also in India, the risk of impoverishment due to CVD was 37% greater than for communicable diseases (95% confidence interval, CI, 1.2 to 1.5).[59]

Impact of stroke

The average OOP burden as a percentage of income in Japan ranged between 5.1-17.2% (*Table 2B*).[33] In China, OOP costs in the first three months after diagnosis of stroke was 158% greater than the annual income. Catastrophic spending (i.e. OOP spending >30% of annual income) was experienced by 71%, pushing an estimated 23% of insured and 62% of uninsured stroke patients below the 1 USD per day poverty line.[49] In the USA, 27.8% of stroke patients reported OOP spending at >20% of the family income.[69] Among Australian stroke survivors, an estimated 473 USD were spent in the first year after diagnosis and 61% perceived financial hardship after 12 months.[57 61]

Impact of cancer

All but five of the 28 studies reporting on cancer originated from high-income countries (*Table 2C*). OOP spending as a percentage of annual income was estimated by two different studies at 9.7% and 44% for breast cancer in the USA.[32 72] In Canada, the percentage was 2.3%.[41] In these countries, perceived financial hardship (e.g. worries about, or change for the worse in, financial situation) for breast cancer was reported by 1-92% of women.[40 41 52] This perception of financial burden was experienced by 70% of breast cancer patients in a study from Pakistan.[18] When comparing early to late expenditures for cervical cancer in Nigeria, the costs rose from 240 to 558 USD.34 Among Norwegian women, income loss for cervical, breast, colon and lung cancer was experienced by 3.8%, 5.7%, 6.2% and 21.1%, respectively. A loss in income due to cervical cancer was reported by 39% of Argentinean women.[71] When comparing cancer to communicable diseases in India, the risk of catastrophic spending, defined as OOP costs exceeding 40% of household income, and the risk of impoverishment was 2.7 times (95% CI 2.1 to 3.1) and 2.3 times (95% CI 1.9 to 2.9) higher.[59]

Of the five studies focusing on coping strategies, all except one did so for the assessment of the impact of cancer.[27 64 68 77] The results of a study by Chirikos and colleagues suggested that losses incurred by breast cancer patients were compensated by other individuals in the household.[64] Income and savings were used to pay for health care in up to 80% of breast cancer patients, 10% increased credit card debt, 7% borrowed from friends or family and 5% left some medical bills unpaid.[77]

Impact of chronic obstructive pulmonary disorder

In Australia, financial hardship (e.g. worries about, or change for the worse in, financial situation) was felt by 36-78% of COPD patients (*Table 2D*).[46 58] Financial catastrophe, at a 10% income threshold, was experienced by 46% of COPD patients. In absolute terms, annual OOP expenditure among COPD sufferers was 2048 USD.[58]

Impact of chronic kidney disease

57% of Australian CKD patients reported financial hardship (*Table 2E)*. Using the same income threshold of 10%, financial catastrophe was experienced by 71% of CKD patients, which is equivalent in absolute terms to annual OOP expenditure of 3755 USD.[56] In Japan, mean annual OOP expenditure was 2604 USD.[48] OOP expenses due to CKD increased by 60% between 2002 and 2005, and 32.6% of CKD patients spent more than 10% on income OOP.[67 69]

Table 2A. Results of the included studies investigating the impact of cardiovascular disease on households and impoverishment.

Study	Type of outcome	Outcome specified as	Assessment type	Point estimate	SD for mean	95% CI	Quality score
Baanders and Heijmans, 2007	Financial burden	Economic consequences perceived by the partners	B coefficient[b]	0.03	NA	NA	3
Banthin and Bernard; 2006	Catastrophic expenditure	>20% of family income, per year	Percent	10.4	NA	NA	8
Engelgau et al; 2012	OOP	Per hospital stay, private + public (1995-1996)	Mean, $	364	NA	NA	7
	OOP	Per hospital stay, private + public (2004)	Mean, $	575	NA	NA	
	Catastrophic expenditure	Patients with CVD and injuries vs CDs	OR	1.12	NA	(0.99 to 1.27)	
	Impoverishment	Patients with CVD and injuries vs CDs	OR	1.37	NA	(1.23 to 1.53)	
Huffman et al; 2011	Income loss	Decrease in individual income in high income group, in Argentina	Percent	57.3	NA	NA	5
	Income loss	Decrease in household income in high income group, in Argentina	Percent	67.5	NA	NA	
	Catastrophic expenditure	>40% OOP of non-food expenditures and distress financing, in Argentina	Percent	11.0	NA	NA	
	Income loss	Decrease in individual income in high income group, in China	Percent	13.1	NA	NA	
	Income loss	Decrease in household income in high income group, in China	Percent	14.3	NA	NA	
	Catastrophic expenditure	>40% OOP of non-food expenditures and distress financing, in China	Percent	56.6	NA	NA	

Table 2A. Continued

Study	Type of outcome	Outcome specified as	Assessment type	Point estimate	SD for mean	95% CI	Quality score
	Income loss	Decrease in individual income in high income group, in India	Percent	25.1	NA	NA	
	Income loss	Decrease in household income in high income group, in India	Percent	26.3	NA	NA	
	Catastrophic expenditure	>40% OOP of non-food expenditures and distress financing, in India	Percent	82.0	NA	NA	
	Income loss	Decrease in individual income in high income group, in Tanzania	Percent	63.0	NA	NA	
	Income loss	Decrease in household income in high income group, in Tanzania	Percent	63.5	NA	NA	
	Catastrophic expenditure	>40% OOP of non-food expenditures and distress financing, in Tanzania	Percent	84.3	NA	NA	
Okumura and Ito; 2013	OOP	Average OOP burden for IHD + SPD	Percent	11.1	NA	NA	5
	OOP	Average OOP burden for IHD + MPD	Percent	6.6	NA	NA	
	OOP	Average OOP burden for IHD + noncase	Percent	9.5	NA	NA	
Rao et al; 2011	OOP	Household consumption expenditure, per year	Percent	30.0[a]	NA	NA	1
	OOP	OOP per hospitalization	Mean, $	284	NA	NA	

[a] Value adjusted for insurance reimbursement.
[b] Model includes disease characteristics.
CD=communicable diseases, CI=confidence interval, CVD=cardiovascular disease, IHD=ischemic heart disease, MPD=mild psychological distress, NCDs=noncommunicable diseases, NA=not applicable, OOP=out-of-pocket, OR=odds ratio, SD=standard deviation, SPD=serious psychological distress.

Table 2B. Results of the included studies on the impact of stroke on households and impoverishment.

Study	Type of outcome	Outcome specified as	Assessment type	Point estimate	SD for mean	95% CI	Quality score
Banthin and Bernard; 2006	Catastrophic expenditure	>20% of family income, per year	Percent	27.8	NA	NA	8
Dewey et al; 2003	OOP	OOP costs, for first ever stroke, in first year	Mean, $	473	NA	NA	4
	OOP	Indirect costs, for first ever stroke, in first year	Mean, $	900	NA	NA	
	Financial burden	Total costs per case, for first ever stroke, in first year	Mean, $	14593	NA	NA	
Essue et al; 2012	Hardship	Participants that reported hardship after disease	Percent	61.0	NA	NA	4
Gerzeli et al; 2005	Financial burden	Total social costs per patient in, per year	Mean, $[a]	37577	37198	(-35331 to 110486)	3
	Financial burden	Total health care costs per patient, per year	Mean, $[a]	19784	NA	NA	
	Financial burden	Total direct costs per patient, per year	Mean, $[a]	34369	NA	NA	
	Financial burden	Total non-health care costs per patient, per year	Mean, $[a]	14588	NA	NA	
Heeley et al, 2009	OOP	OOP expenses, per year	Mean, $[a]	9230	10061	(-10489 to 28951)	4
	OOP	OOP expenses in the first 3 months as a proportion of total annual income	Percent	158	NA	NA	
	Catastrophic expenditure	>30% family income, per year	Percent	71.0	NA	NA	

Table 2B. Continued

Study	Type of outcome	Outcome specified as	Assessment type	Point estimate	SD for mean	95% CI	Quality score
	Impoverishment	Patients with income above the poverty line and moved below the poverty line due to OOP[b]	Percent	37.0	NA	NA	
Kang et al; 2011	Financial burden	Per person annual costs of nonfatal stroke in first year, for men	Mean, $	5545	NA	NA	NA
	Financial burden	Per person annual costs of nonfatal stroke in first year, for women	Mean, $	4483	NA	NA	
	Financial burden	Costs of fatal stroke, for men	Mean, $	7981	NA	NA	
	Financial burden	Costs of fatal stroke, for women	Mean, $	42171	NA	NA	
	OOP	Per person annual OOP costs of nonfatal stroke in first year, for men and women	Mean, $	1490	NA	NA	
McKevitt et al, 2011	Income loss	Reported income loss, per patient	Percent	18	NA	NA	7
Okumura and Ito; 2013	OOP	Average OOP burden for stroke + MPD	Percent	5.1	NA	NA	5
	OOP	Average OOP burden for stroke + noncase	Percent	7.4	NA	NA	
	OOP	Average OOP burden for stroke + SPD	Percent	17.2	NA	NA	

[a] Per month or per quarter means and SD were recalculated to annual values to make the eligible studies better comparable. Per month mean and SD: times 12; per quarter mean and SD: times 4.
[b] Poverty line defined as US$ 1,00/day.
CI=confidence interval, MPD=mild psychological distress, NA=not applicable, OOP=out-of-pocket, SD=standard deviation, SPD=serious psychological distress.

Table 2C. Results of the included studies on the impact of cancers on households and impoverishment.

Study	Type of outcome	Outcome specified as	Assessment type	Point estimate	SD for mean	95% CI	Reported NCD	Quality score
Arozullah et al; 2004	OOP	Direct medical cost, per year	Mean, $[a]	8833	14249	(-19094 to 36761)	Breast cancer	2
	OOP	Direct medical cost ratio	Percent	24.0b	82.0	NA	Breast cancer	
	OOP	Direct non-medical cost, per year	Mean, $[a]	1938	335	(-4644 to 8521)	Breast cancer	
	OOP	Direct non-medical cost ratio	Percent	3.0b	5.0	NA	Breast cancer	
	OOP	Indirect cost, per year	Mean, $[a]	10757	29652	(-47361 to 68875)	Breast cancer	
	OOP	Indirect medical cost ratio	Percent	17.0b	37.0	NA	Breast cancer	
	OOP	Total OOP and lost income costs, per year	Mean, $[a]	21528	35008	(21528 to 35008)	Breast cancer	
	OOP	Total OOP and lost income costs	Percent	44.0b	94.0	NA	Breast cancer	
Arrossi et al; 2007	Income loss	Loss of family income, for patient	Percent	39.0	NA	NA	Cervical cancer	4
	Income loss	Loss of family income, for caregiver	Percent	16.0	NA	NA	Cervical cancer	
	Income loss	Loss of family income vs non compliance	OR	3.1	NA	(1.4 to 7)	Cervical cancer	
Banthin and Bernard; 2006	Catastrophic expenditure	>20% of family income, per year	Percent	6.7	NA	NA	Colon cancer	8
Bennett et al, 2009	Hardship	Continued to work at the same level	Percent	61	NA	NA	Breast cancer	6
	Hardship	Worked less or quit work	Percent	11	NA	NA	Cervical cancer	

Table 2C. Continued

Study	Type of outcome	Outcome specified as	Assessment type	Point estimate	SD for mean	95% CI	Reported NCD	Quality score
	Hardship	Continued to work at the same level	Percent	10	NA	NA	Colon cancer	
	Hardship	Worked less or quit work	Percent	NA	NA	NA	Colon cancer	
	Hardship	Reported at least one type of economizing	Percent	72	NA	NA	Cancer	
Chirikos et al, 2002a	Income loss	Total household income growth in newly impaired women, between 1995-2000 (lowest quartile value)	Percent	37	NA	NA	Breast cancer	8
	Income loss	Total household income growth in other women, between 1995-2000 (lowest quartile value)	Percent	22	NA	NA	Breast cancer	
	OOP	Above average medical expenses in newly impaired women	Percent	41	NA	NA	Breast cancer	
	OOP	Above average medical expenses in in other women	Percent	20	NA	NA	Breast cancer	
Chirikos et al, 2002b	Income loss	Household income in breast cancer group, change over 5 years	Mean, $	-5	21	NA	Breast cancer	7
	Income loss	Household income in control group, change over 5 years	Mean, $	10	21	NA	Breast cancer	
	Income loss	Value of household assets in breast cancer group, change over 5 years	Mean, $	82	169	NA	Breast cancer	
	Income loss	Value of household assets in control group, change over 5 years	Mean, $	118	204	NA	Breast cancer	

Table 2C. Continued

Study	Type of outcome	Outcome specified as	Assessment type	Point estimate	SD for mean	95% CI	Reported NCD	Quality score
Davidoff et al; 2013	OOP	Total OOP per income	Percent	23.9	NA	NA	Cancer	9
	Catastrophic expenditure	>20% income	Percent	27.6	NA	NA	Cancer	
	OOP	OOP expenditure, per year	Mean, $	3850	NA	NA	Lung cancer	
	OOP	OOP expenditure, per year	Mean, $	4600	NA	NA	Breast cancer	
	OOP	OOP expenditure, per year	Mean, $	4200	NA	NA	Colon cancer	
Eaker et al; 2011	Income loss	Income increase >20%, women with breast cancer	Percent	30.6	NA	NA	Breast cancer	7
	Income loss	Income increase >20%, women without breast cancer	Percent	32.4	NA	NA	Breast cancer	
	Income loss	Income increase >20%, adjusted for education	Risk Ratio	0.99	NA	(0.96 to 1.01)	Breast cancer	
Engelgau et al; 2012	OOP	Per hospital stay, private + public (1995-1996)	Mean, $	307	NA	NA	Cancer	7
	OOP	Per hospital stay, private + public (2004)	Mean, $	498	NA	NA	Cancer	
	Catastrophic expenditure	Patients with cancer vs CD	OR	2.7	NA	(2.1 to 3.1)	Cancer	
	Impoverishment	Patients with cancer vs CD	OR	2.3	NA	(1.9 to 2.9)	Cancer	
Gordon et al; 2007	Financial Burden	Indirect costs	Mean, $[a]	5036	7221	(-9117 to 19191)	Breast cancer	3

Table 2C. Continued

Study	Type of outcome	Outcome specified as	Assessment type	Point estimate	SD for mean	95% CI	Reported NCD	Quality score
	Financial Burden	Direct costs	Mean, $[a]	2311	3830	(-5196 to 9819)	Breast cancer	
	Financial Burden	Total costs, per year	Mean, $a	3730	5591	(-7729 to 14690)	Breast cancer	
	Hardship	Reported any type of economic loss	Percent	92.0	NA	NA	Breast cancer	
Gordon et al, 2009	OOP	Net costs (e.g. drugs, transport, consultation)	Mean, $	5938	NA	(4930 to 6946	Breast cancer	5
Lauzier et al; 2008	Income loss	Wage losses for both absences and reduced hours of work, per year	Mean, $	10101	20672	(-28039 to 46661)	Breast cancer	6
	Hardship	Reported hardship after diagnosis	Percent	14.7	NA	NA	Breast cancer	
Lauzier et al, 2011	OOP	Total net cost (considering financial assistance received	Mean, $	330	301	NA	Breast cancer	6
Lauzier et al; 2013	OOP	Absolute net OOP costs (costs minus financial assistance)	Mean, $[a]	1333	1209	(-1036 to 3703)	Breast cancer	7
	OOP	% OOP of family income, per year	Percent	2.3	NA	NA	Breast cancer	
	Hardship	Change for the worse in family financial situation 1 year after diagnosisc	Percent	1.0	NA	NA	Breast cancer	
	Hardship	Low OOP costs and high wage losses	Percent	2.5	NA	(1.9 to 3.3)	Breast cancer	
	Hardship	High OOP costs and low wage losses	Percent	1.3	NA	(0.9 to 2.0)	Breast cancer	

Table 2C. Continued

Study	Type of outcome	Outcome specified as	Assessment type	Point estimate	SD for mean	95% CI	Reported NCD	Quality score
	Hardship	High OOP costs and high wage losses	Percent	2.2	NA	(1.6 to 3.1)	Breast cancer	
Longo and Bereza; 2011	OOP	Total OOP costs for lung, colon and prostate cancer, per year	Mean, $[a]	1856	3302	(-4615 to 8328)	Cancer	5
	OOP	Total OOP costs, per year	Mean, $[a]	4876	10311	(-15334 to 25088)	Breast cancer	
Markman and Luce, 2010	OOP	Total OOP costs <5000$	Percent	60	NA	NA	Breast cancer	4
	OOP	Total OOP costs, >5000$	Percent	41	NA	NA	Breast cancer	
	OOP	Total OOP costs, <5000$	Percent	52	NA	NA	Colon cancer	
	OOP	Total OOP costs, >5000$	Percent	46	NA	NA	Colon cancer	
	OOP	Total OOP costs, <5000$	Percent	56	NA	NA	Lung cancer	
	OOP	Total OOP costs, >5000$	Percent	44	NA	NA	Lung cancer	
	Hardship	Reported large financial stress caused by cost	Percent	19	NA	NA	Breast cancer	
	Hardship	Reported large financial stress caused by cost	Percent	25	NA	NA	Colon cancer	
	Hardship	Reported large financial stress caused by cost	Percent	27	NA	NA	Lung cancer	
Moore, 1999	OOP	Total costs (e.g. assistance, drugs, households improvements)	Mean, $	503	484	NA	Breast cancer	

Table 2C. Continued

Study	Type of outcome	Outcome specified as	Assessment type	Point estimate	SD for mean	95% CI	Reported NCD	Quality score
Obi and Ozumba, 2008	Financial burden	Early expenditures by patients (e.g. initial visit, preliminary investigations and treatment)	Mean, $	240	NA	NA	Cervical cancer	3
	Financial burden	Late expenditures by patients (e.g. transportation, hospital admission, treatment))	Mean, $	558	NA	NA	Cervical cancer	
Pisu et al; 2011	OOP	Direct OOP cost, per year	Mean, $[a]	4105	5344	(-6369 to 14579)	Breast cancer	4
	OOP	Family income spent on total OOP costs, per year	Percent	9.7	NA	NA	Breast cancer	
Shankaran et al, 2012	Income loss	>20% income decline	Percent	23.9	NA	NA	Colon cancer	5
	Hardship	Borrowed money from family/ friends	Percent	16	NA	NA	Colon cancer	
	Hardship	Withdrew money from saving accounts	Percent	30	NA	NA	Colon cancer	
	Hardship	Withdrew money from retirement account	Percent	15	NA	NA	Colon cancer	
Shugarman et al; 2007	Financial burden	Total payment for beneficiaries with cancer, in the last year of life	Mean, $	37708	NA	NA	Colon cancer	3
Syse and Tonnessen; 2012	Income loss	Percent wise income deviation from reference category, for men[d]	Percent	-7.2	1.7	(-10.6 to -3.6)	Colon cancer	9
	Income loss	Percent wise income deviation from reference category, for women[d]	Percent	-6.1	1.8	(-9.7 to -2.3)	Colon cancer	

Table 2C. Continued

Study	Type of outcome	Outcome specified as	Assessment type	Point estimate	SD for mean	95% CI	Reported NCD	Quality score
	Income loss	Percent wise income deviation from reference category, for men[d]	Percent	-21.1	3.6	(-27.3 to -12.2)	Lung cancer	
	Income loss	Percent wise income deviation from reference category, for women[d]	Percent	-20.0	3.4	(-27.8 to -13.7)	Lung cancer	
	Income loss	Percent wise income deviation from reference category, for women[d]	Percent	-5.7	0.8	(-7.2 to -4.2)	Breast cancer	
	Income loss	Percent wise income deviation from reference category[d]	Percent	-3.8	1.5	(-6.7 to -0.9)	Cervical cancer	
Van Houtven et al; 2010	Financial burden	Total economic burden for informal caregivers, in any disease phase	Mean, $	16778	NA	NA	Lung and colorectal cancer	5
	Financial burden	Total time costs for informal caregivers, in any disease phase	Mean, $	15057	NA	NA	Lung and colorectal cancer	
	OOP	Total OOP costs for informal caregivers, in any disease phase	Mean, $	1483	NA	NA	Lung and colorectal cancer	
Yabroff et al, 2008	OOP	Net costs of care, in the first 12 months, for men	Mean, $	32044	NA	(31330 to 32758)	Colorectal cancer	6
	OOP	Net costs of care, in the last 12 months of life, for men	Mean, $	39484	NA	(38682 to 40286)	Colorectal cancer	
	OOP	Net costs of care, in the first 12 months, for men	Mean, $	38606	NA	(37339 to 39873)	Lung cancer	

Table 2C. Continued

Study	Type of outcome	Outcome specified as	Assessment type	Point estimate	SD for mean	95% CI	Reported NCD	Quality score
	OOP	Net costs of care, in the last 12 months of life, for men	Mean, $	56013	NA	(55076 to 56950)	Lung cancer	
	OOP	Net costs of care, in the first 12 months, for women	Mean, $	32392	NA	(31798 to 32987)	Colorectal cancer	
	OOP	Net costs of care, in the last 12 months of life, for women	Mean, $	36374	NA	(35659 to 37090)	Colorectal cancer	
	OOP	Net costs of care, in the first 12 months, for women	Mean, $	37693	NA	(36681 to 38705)	Lung cancer	
	OOP	Net costs of care, in the last 12 months of life, for women	Mean, $	55004	NA	(54039 to 55971)	Lung cancer	
	OOP	Net costs of care, in the first 12 months, for women	Mean, $	12693	NA	(12460 to 12925)	Breast cancer	
	OOP	Net costs of care, in the last 12 months of life, for women	Mean, $	31601	NA	(31133 to 32068)	Breast cancer	
Zaidi et al; 2012	Hardship	Cost more than anticipated	Percent	70.0	NA	NA	Breast cancer	4
	Hardship	Perceived level of burden unmanageable	Percent	70.0	NA	NA	Breast cancer	
Zhou et al, 2008	OOP	Total drug costs, patients with social health insurance	Median, $	1028	NA	NA	Breast cancer	6
	OOP	Total drug costs, patients without social health insurance	Median, $	231	NA	NA	Breast cancer	
	OOP	Total drug costs, patients with social health insurance	Median, $	1829	NA	NA	Lung cancer	
	OOP	Total drug costs, patients without social health insurance	Median, $	1289	NA	NA	Lung cancer	

Table 2C. Continued

Study	Type of outcome	Outcome specified as	Assessment type	Point estimate	SD for mean	95% CI	Reported NCD	Quality score
	OOP	Total drug costs, patients with social health insurance	Median, $	1730	NA	NA	Colorectal cancer	
	OOP	Total drug costs, patients without social health insurance	Median, $	1301	NA	NA	Colorectal cancer	

[a] Per month or per quarter means and SD were recalculated to annual values to make the eligible studies better comparable. Per month mean and SD: times 12; per quarter mean and SD: times 4.
[b] Costs were adjusted for income.
[c] Reference low OOP costs and low wage losses.
[d] The modeled income for the reference categories are $36100 for women and $39200 for men, respectively.
CD=communicable diseases, CI=confidence interval, NCDs=noncommunicable diseases, NA=not applicable, OOP=out-of-pocket, OR=odds ratio, SD=standard deviation.

Table 2D. Results of the included studies on the impact of chronic obstructive pulmonary disorder on households and impoverishment.

Study	Type of outcome	Outcome specified as	Assessment type	Point estimate	SD for mean	95% CI	Quality score
Baanders and Heijmans, 2007	Financial burden	Economic consequences perceived by the partners	B coefficient [b]	0.01	NA	NA	3
Essue et al; 2011	Hardship	Participants that experienced economic hardship after disease	Percent	78.0	NA	NA	4
	Catastrophic expenditure	>10% family income, in previous 3 months	Percent	46.0	NA	NA	
	OOP	OOP spending per year	Mean [a]	2048	2767	(-3376 to -7473)	
	OOP	Reported used financial coping strategy	Percent	65.0	NA	NA	
Jeon et al, 2009	Hardship	Affordability of treatment (e.g. capacity to pay for medications, consultations)	Percent	36	NA	NA	6
	Hardship	Affordability of other things (e.g. capacity to pay for basic living expenses, transport, food)	Percent	38	NA	NA	

[a] Per month or per quarter means and SD were recalculated to annual values to make the eligible studies better comparable. Per month mean and SD: times 12; per quarter mean and SD: times 4.
[b] model includes disease characteristics.
CI=confidence interval, NA=not applicable, OOP=out-of-pocket, SD=standard deviation.

Table 2E. Results of the included studies on the impact of chronic kidney disease on households and impoverishment.

Study	Type of outcome	Outcome specified as	Assessment type	Point estimate	SD for mean	95% CI	Quality score
Banthin and Bernard; 2006	Catastrophic expenditure	>10% of family income, per year	Percent	19.7	NA	NA	8
	Catastrophic expenditure	>20% of family income, per year	Percent	9.8	NA	NA	
Campbell et al; 2011	OOP	Increase in OOP spending from 2002 to 2005	Percent	60.0	NA	NA	5
Essue et al; 2013	Hardship	Participants that experienced economic hardship after disease	Percent	57.0	NA	NA	3
	Catastrophic expenditure	>10% of family income, per 3 months	Percent	71.0	NA	NA	
	OOP	OOP spending for all participants, per year	Mean, $[a]	3755	4430	(-4928 to 12439)	
Higashiyama et al; 2009	Financial burden	Total medical expenditure/ person	Mean, $	7755	NA	NA	7

[a] Per month or per quarter means and SD were recalculated to annual values to make the eligible studies better comparable. Per month mean and SD: times 12; per quarter mean and SD: times 4.
CI=confidence interval, NA=not applicable, OOP=out-of-pocket, SD=standard deviation.

Impact of type 2 diabetes mellitus

From the 21 studies focusing on type DM, eight originated from India and showed a consistent impact on households (*Table 2F*). Mean OOP expenditure per in-patient hospital stay for DM increased from 134 USD to 211 USD between 1995 and 2004 and direct total OOP spending per year was estimated at 262-280 USD.[29,50,59] The percent wise household consumption spent OOP ranged between 7.7-17.5%.[26,30] In Japan, the average OOP burden for DM, as a percentage of household income, ranged from 4.8% to 11.3%.[33]

In the USA, the mean annual OOP diabetes care cost was 1237 USD and increased by 23% from 2002 to 2005.[28,67] Nearly 40% of DM cases in the USA experienced catastrophic spending (using the >10% threshold); 13% experienced catastrophic spending even above the 20% threshold.[69] A cross-country analysis, performed by Niens et al, quantified the impoverishing effects of purchasing medicines for different diseases, including DM. Buying lowest price generic or originator brand glibenclamide would plunge either 2 million (5%) or 3 million (10%) chronic patients below the 1.25 USD/day poverty line, respectively. When stratifying across the 16 countries, these percentages ranged between 0 and 58%.[35]

Impact of NCDs combined

The proportion spent OOP on NCDs increased from 31.6% to 47.3% between 1995 and 2004 in India (*Table 2G*).[59] In Japan, the average OOP burden was 2.1% of available income.[33] The threshold for what is considered 'catastrophic spending' has a large impact on the proportion of households who experience it. For example, in Burkina Faso, the proportion of households experiencing catastrophic spending gradually increased from 4.5% to 10.6% (and in absolute numbers from 79 to 108 USD annually) as the catastrophic threshold lowered, stepwise, from >60% to >40%, >30%, and >20%.[24] The mean NCD expenditure as a proportion of household capacity to pay in Vietnam was 27.7%. When using different catastrophic spending thresholds, nearly 60% of the participants spent between 20-30% of their income on NCDs.[21]

Table 2F. Results of the included studies on the impact of type 2 diabetes mellitus on households and impoverishment.

Study	Type of outcome	Outcome specified as	Assessment type	Point estimate	SD for mean	95% CI	Quality score
Baanders and Heijmans, 2007	Financial burden	Economic consequences perceived by the partners	B coefficient [f]	0.03	NA	NA	3
Banthin and Bernard; 2006	Catastrophic expenditure	>20% of family income, per year	Percent	13.0	NA	NA	8
Campbell et al; 2011	OOP	Increase in OOP spending from 2002 to 2005	Percent	23.0	NA	NA	5
Chang; 2010	OOP	Inpatient costs	Mean, $[a]	133	583	(1010 to 1276)	5
	OOP	Outpatient costs	Mean, $[a]	10	11	(-11 to 32)	
Chatterjee et al, 2011	Financial burden	Monetary value of informal care, by opportunity cost method	Mean, $	34	NA	NA	5
	Financial burden	Monetary value of informal care, by proxy good method	Mean, $	35	NA	NA	
Engelgau et al; 2012	OOP	Per hospital stay, private + public (1995-1996)	Mean, $	134	NA	NA	7
	OOP	Per hospital stay, private + public (2004)	Mean, $	211	NA	NA	
Falconer et al, 2010	OOP	Prescription medication, per year	Mean, $	31	NA	NA	2
	OOP	Over-the-counter medications	Mean, $	64	NA	NA	
Goldhaber-Fiebert et al, 2010	OOP	OOP (uninsured) as a % of total health expenditure, in India	Percent	75	NA	NA	4
	OOP	OOP (uninsured) as a % of total health expenditure, in China	Percent	51	NA	NA	
	OOP	OOP (uninsured) as a % of total health expenditure, in Thailand	Percent	19	NA	NA	

Table 2F. Continued

Study	Type of outcome	Outcome specified as	Assessment type	Point estimate	SD for mean	95% CI	Quality score
	OOP	OOP (uninsured) as a % of total health expenditure, in Malaysia	Percent	38	NA	NA	
Grover et al, 2005	OOP	Direct costs, per year (e.g. drugs, transport, consultations)	Mean, $	280	239	NA	4
	OOP	Indirect costs, per year (e.g. loss of income, days lost because of illness for patient and caregivers)	Mean, $	113	273	NA	
Jeon et al, 2009	Hardship	Affordability of treatment (e.g. capacity to pay for medications, consultations)	Percent	50	NA	NA	6
	Hardship	Affordability of other things (e.g. capacity to pay for basic living expenses, transport, food)	Percent	48	NA	NA	
Joshi et al; 2013	OOP	Cost every doctor visit for DM	Mean, $[a]	4	2	(0 to 8)	2
Khowaja et al, 2007	OOP	Total direct costs (e.g. drugs, travel, investigations)	Mean, $	221	NA	NA	4
	OOP	Total indirect costs (e.g. loss of time and productivity)	Mean, $	22	NA	NA	
Niens et al; 2010	Impoverishment	Absolute impoverishment in chronic patient population, due to purchase of LPG glibenclamide, 16 countries	Count	2000000	NA	NA	NA
	Impoverishment	Relative impoverishment in chronic patient population, due to purchase of LPG glibenclamide, 16 countries[b]	Percent	5.0	NA	NA	
	Impoverishment in Kyrgyzstan	Population that will fall below poverty line after purchasing LPG glibenclamide[b]	Percent	2.0	NA	NA	

Table 2F. Continued

Study	Type of outcome	Outcome specified as	Assessment type	Point estimate	SD for mean	95% CI	Quality score
	Impoverishment in Mali	Idem above	Percent	53.0	NA	NA	
	Impoverishment in Nigeria	Idem above	Percent	71.0	NA	NA	
	Impoverishment in Pakistan	Idem above	Percent	0	NA	NA	
	Impoverishment in Tajikistan	Idem above	Percent	11.0	NA	NA	
	Impoverishment in Tanzania	Idem above	Percent	58.0	NA	NA	
	Impoverishment in Uganda	Idem above	Percent	53.0	NA	NA	
	Impoverishment in Uzbekistan	Idem above	Percent	22.0	NA	NA	
	Impoverishment in Yemen	Idem above	Percent	10.0	NA	NA	
	Impoverishment in El Salvador	Idem above	Percent	11.0	NA	NA	
	Impoverishment in Indonesia	Idem above	Percent	0	NA	NA	
	Impoverishment in Jordan	Idem above	Percent	0	NA	NA	
	Impoverishment in Mongolia	Idem above	Percent	6.0	NA	NA	
	Impoverishment in Peru	Idem above	Percent	5.0	NA	NA	

Table 2F. Continued

Study	Type of outcome	Outcome specified as	Assessment type	Point estimate	SD for mean	95% CI	Quality score
	Impoverishment in Philippines	Idem above	Percent	13.0	NA	NA	
	Impoverishment in Tunisia	Idem above	Percent	0	NA	NA	
Okumura and Ito; 2013	OOP	Average OOP burden for diabetes + SPD	Percent	11.3	NA	NA	5
	OOP	Average OOP burden for diabetes + MPD	Percent	4.8	NA	NA	
	OOP	Average OOP burden for diabetes + noncase	Percent	6.4	NA	NA	
Rayappa et al, 1999	OOP	Total direct costs for non -hospitalized patients	Mean, $	262	NA	NA	7
Ramachandran et al, 2007	Income	Family income in urban area, per year	Median, $	58	NA	NA	5
	Income	Family income in rural area, per year	Median, $	21	NA	NA	
	Financial burden	Total expenditure on health in urban area (e.g. medication, consultations)	Median, $	6	NA	NA	
	Financial burden	Total expenditure on health in rural area (e.g. medication, consultations)	Median, $	3	NA	NA	
Rao et al; 2011	OOP	OOP household consumption expenditure, per year[c]	Percent	17.0	NA	NA	1
	OOP	OOP per hospitalization	Mean, $	137	NA	NA	

Table 2F. Continued

Study	Type of outcome	Outcome specified as	Assessment type	Point estimate	SD for mean	95% CI	Quality score
Rodbard et al; 2010	OOP	Health care OOP expenses, per year[d]	B coefficient	247.9	NA	(129.4 to 335.7)	6
	OOP	Health care OOP expenses, per year[e]	Mean, $	1237	NA	NA	
Shobhana et al, 2000	Income	Family income in private hospital, per year	Mean, $	1546	NA	NA	3
	Income	Family income in public hospital, per year	Mean, $	309	NA	NA	
	OOP	Income spent on DM, by inpatient care	Percent	17.5	NA	NA	
	OOP	Income spent on DM, by outpatient care	Percent	7.7	NA	NA	

[a] Per month or per quarter means and SD were recalculated to annual values to make the eligible studies better comparable. Per month mean and SD: times 12; per quarter mean and SD: times 4.
[b] Poverty line defined as US$ 1,25 USD/day.
[c] Value adjusted for insurance reimbursement.
[d] No diabetes as reference group.
[e] No diabetes as reference group and value adjusted for annual health care.
[f] model includes disease characteristics.
CI=confidence interval, DM=diabetes mellitus, LPG=lowest price generic, MPD=mild psychological distress, NA=not applicable, OOP=out-of-pocket, SD=standard deviation, SPD=serious psychological distress.

Table 2G. Results of the included studies investigating the impact of noncommunicable diseases on households and impoverishment.

Study	Type of outcome	Outcome specified as	Assessment type	Point estimate	SD for mean	95% CI	Quality score
Engelgau et al; 2012	OOP	Per capita household income spent on OOP expenses for healthcare, poorest (2004)	Percent	3.8	NA	NA	7
	OOP	Per capita household income spent on OOP expenses for healthcare, richest (2004)	Percent	6.6	NA	NA	
	OOP	% of OOP expenses spent on NCD (1995-1996)	Percent	31.6	NA	NA	
	OOP	% of OOP expenses spent on NCD (2004)	Percent	47.3	NA	NA	
Okumura and Ito; 2013	OOP	Average OOP burden	Percent	2.1	6.2	NA	5
Su et al; 2006	Catastrophic expenditure	Prevalence of catastrophic (>20% of monthly non-food expenditure)	Percent	10.6	NA	NA	1
	Catastrophic expenditure	Prevalence of catastrophic (>40% of monthly non-food expenditure)	Percent	6.1	NA	NA	
	OOP	Household health expenditure, per year (>20% of non-food expenditure)	Mean, $[a]	79	130	(-177 to 335)	
	OOP	Household health expenditure, per year (>40% of non-food expenditure)	Mean, $[a]	96	150	(-198 to 391)	
Sun et al; 2009	Financial burden	Chronic disease expense per capita / annual non-food expenditure, Shandong, insured members	Percent	27.0	NA	NA	2

Table 2G. Continued

Study	Type of outcome	Outcome specified as	Assessment type	Point estimate	SD for mean	95% CI	Quality score
	Financial burden	Chronic disease expense per capita / annual non-food expenditure, Shandong, uninsured members	Percent	47.0	NA	NA	
	Financial burden	Average chronic disease expense per capita / annual nonfood expenditure, Ningxia, insured members	Percent	35.0	NA	NA	
	Financial burden	Average chronic disease expense per capita / annual nonfood expenditure, Ningxia, uninsured members	Percent	42.0	NA	NA	
	Catastrophic expenditure	>40% Shandong, insured members, per year	Percent	15.0	NA	NA	
	Catastrophic expenditure	>40% Shandong, uninsured members, per year	Percent	21.0	NA	NA	
	Catastrophic expenditure	>40% Ningxia, insured members, per year	Percent	14.0	NA	NA	
	Catastrophic expenditure	>40% Ningxia, uninsured members, per year	Percent	18.0	NA	NA	
Thuan et al; 2006	Financial burden	Health expenditure spend on NCDs	Percent	27.7	NA	NA	1
	Catastrophic expenditure	Total household health expenditures to household capacity to pay between 20-30%	Ratio	23.4	NA	NA	
	Catastrophic expenditure	Percentage of health expenditure spent on NCDs	Ratio	27.7	NA	NA	

[a] Per month or per quarter means and SD were recalculated to annual values to make the eligible studies better comparable. Per month mean and SD: times 12; per quarter mean and SD: times 4.
CI=confidence interval, NCDs=noncommunicable diseases, NA=not applicable, OOP=out-of-pocket, SD=standard deviation.

DISCUSSION

This systematic review summarizes 64 studies published worldwide of the impact of the major NCDs (CHD, stroke, COPD, major cancers, DM and CKD) at the micro-economic level on households and impoverishment. The studies show a steady global increase in household expenditure on NCDs between 1999 and 2014. The importance of these trends in global health is further underlined by the 'WHO Global Action Plan for the Prevention of Non-communicable Diseases 2013-2020', which highlights the need for further research into NCDs and their impact at the micro-economic level.[81]

There is evidence that a substantial number of people experience financial hardship due to NCDs, as income losses affect patients and their caregivers and OOP medical expenditure for NCDs drive households into financial catastrophe and impoverishment. This rising burden is directly related to the global rise of NCDs, particularly in LMIC, many of which have under-resourced healthcare systems that impose OOP payments on individuals and households as a means to supplement other sources of revenue.[1] As healthcare systems in LMIC often experience a dual burden of infectious and chronic disease, they are less able to allocate resources towards primary prevention of NCDs. Most eligible studies used OOP expenditure to quantify the magnitude of the economic impact of NCDs on households and for mapping the extent of financial catastrophe, in particular. OOP expenditure was self-reported in most of the studies, with some exceptions where studies used health insurance claim data. Relative to different income proxies, OOP expenditure ranged widely between 2 and 158% across different NCDs and countries.

The threshold for what is considered 'catastrophic spending' has a large impact on the proportion of households who experience it; depending on the income threshold taken by the study, the global proportion of households suffering from financial catastrophe ranged from 6 to 84%. Heterogeneity in the use of an income threshold in combination with differences in study samples (among others, related to insurance coverage levels) undermine comparability across the studies, although evidence does suggest that financial catastrophe due to NCDs is an important issue for all countries and across all income strata. This observation is in accordance with other reports that took a broader (chronic) illness perspective.[8 10 14 82] Variations in OOP spending and financial catastrophe across and within countries depend a great deal on the triad of factors, described by Xu and colleagues, as poverty levels, healthcare service access and use, and the presence or absence of financial risk pooling mechanisms such as health insurance or taxed-based systems.[9] Although it was outside the scope of this study to review the impact of this triad on catastrophic spending, these factors are very likely to be key components of the (varying) relation between OOP spending and catastrophic spending. Therefore, although OOP spending and financial catastrophe are valuable methodological approaches to provide insights into the impact on households, these measures cannot be interpreted without being placed within the specific health system perspective from which the

sample is drawn. Standardized definitions and thresholds would facilitate unbiased and cross-country comparisons.

A minority of the studies addressed the absolute impoverishing effects of NCDs. A large study by Niens et al, in 16 LMICs, showed that the purchase of lowest price generic medication rather than originator brand DM (and other) medication could reduce absolute impoverishment, at the 1.25 USD/day poverty line, from 11% to 6% of the total population. This finding reinforces the need to improve availability of low-priced generics, which for NCDs receives comparatively little attention compared to infectious disease treatment.[83 84]

The extent to which NCDs drive households into relative poverty were more difficult to estimate from the eligible studies, partly due to the fact that relative poverty is more difficult to measure and the definitions are less clear. We observed that some eligible studies used income losses to estimate the relative impoverishing influence of NCDs. For instance, for Norwegian women suffering from cervical, breast or lung cancer, the percent-wise income deviation compared to healthy women was 3.8%, 5.7% and 20% respectively.[22] Household income losses after CVD diagnosis were 67.5%, 14.3%, 26.3% and 63.5% in high-income groups in Argentina, China, India and Tanzania respectively, and were even higher in the lower income groups.[47] These findings are consistent with similar studies, which showed that poor households are less able to cope with healthcare costs compared to more affluent households.[9 85 86] Solely five eligible studies provided insights in the coping strategies adopted by households to cope with a family member suffering from NCDs. The paucity of evidence regarding coping strategies, together with the significant role that illness perceiving and absence of health care seeking due to financial reasons play, are likely to reflect a considerable underestimation of the true extent to which NCDs impact households.

Findings of this systematic review generally concur with and further extend previous reviews on this topic. Previous work was focused on specific types of NCDs, was focused in specific regions of the world or provided methodological commentaries.[10 87-100] A recent narrative review emphasized the importance of standardized definitions for out-of-pocket spending, the use of larger sample sizes and prospective study designs and a better collecting of data on economic consequences of NCDs (i.e. direct and indirect costs).[89] Kankeu and colleagues assessed financial burden of four domains of NCDs (cancers, CVD, COPD, and diabetes) but did not include chronic kidney disease in their review. In addition and interestingly, they included only studies conducted in LMICs.[91] Mahal and colleagues summarized the economic impact of NCDs for India.[94] A second study, conducted by Engelgau and colleagues, non-systematically reviewed studies mostly conducted in India.[10]
Costs involved in cancer care, without stratifying for cancer type, were reviewed in three domains in a systematic review by Pearce and colleagues. The domains included cost-effectiveness and cancer treatment, the indirect cancer costs and human costs of cancer.

Definite conclusions were missing due to conceptual and methodological limitations of the included studies. Nevertheless, the complexity of the costs attached to cancer care was observed.[95] Pisu and colleagues reviewed OOP expenses in breast cancer patients only.[96] Tong and colleagues thematically synthesized patient and caregiver perspectives in CKD. Out of 26 included studies in this review, one study from Thailand focused on economic consequences, and found a large economic strain due to forced early retirement.[97]
Coping with out-of-pocket health payments was assessed in 15 African countries and showed that borrowing and selling assets was an important coping mechanism, its prevalence ranging from 23-68%. Unfortunately a specification of the included diseases was not provided.[93]

The strengths and limitations of our work merit careful consideration. An important strength of this review is the exhaustive search for relevant articles. We used extensive, precise search terms and applied stringent inclusion criteria, specifically the exclusion of studies focusing solely on 'chronic diseases' or 'illness'. We believe that this specific approach gave rise to a comprehensive undiluted perspective of the micro-economic impact of NCDs, since all available evidence was gathered via the initial search and was supplemented by an extensive screening of reference lists for possibly missed eligible studies. However, we do emphasize that precisely defining included chronic illnesses would greatly benefit future research and the disease specific policy implications this research could give rise to.

The methods used by the eligible studies to measure household impact and impoverishment were remarkably heterogeneous which, along with a broader disease burden perspective than NCDs, is a recurrent challenge in similar reviews and did not allow us to pool the reported estimates in a meta-analysis.[14 91] Furthermore, in many studies convenience sampling was used to assemble study samples, and the overall quality of the included studies was moderate to low. Therefore, country-wide and disease-specific implications of the results must be interpreted with caution. Given the already wide scope of our systematic evaluation, we were unable to explore wider impacts associated with NCDs such as non-economic and indirect impacts including educational dropout among children, healthcare utilization and costs of premature death. Estimation of the number and experiences of marginalized and vulnerable people who do not seek care for NCDs for financial reasons is currently neglected and their inclusion could give a more comprehensive overview of the impact of NCDs on households and impoverishment.

CONCLUSIONS

NCDs impose a large and growing global impact on households and impoverishment, in all continents and levels of income. The true extent, however, remains difficult to determine due to heterogeneity across existing studies in terms of populations evaluated, outcomes reported and measures employed. The impact that NCDs exert on households and impoverishment is likely to be underestimated since important economic domains, such as coping strategies and the inclusion of marginalized and vulnerable people who do not seek health care due to financial reasons, are overlooked in literature. Given the scarcity of information on specific regions, further research is required to estimate impact of the separate NCDs on households and impoverishment in LMIC, especially the Middle Eastern, African and Latin American regions.

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Disclosures

With regard to potential conflicts of interest, there is nothing to disclose.

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Appendix 1.
Search strategy 6 November 2014.

('non communicable disease'/de OR 'ischemic heart disease'/exp OR 'cerebrovascular accident'/exp OR 'chronic obstructive lung disease'/de OR 'lung cancer'/exp OR 'colon cancer'/exp OR 'breast cancer'/exp OR 'chronic kidney disease'/de OR 'non insulin dependent diabetes mellitus'/de OR 'uterine cervix cancer'/exp OR ('non communicable' OR noncommunicable OR ((heart OR cardiac OR cardial OR cardiopath* OR cardiomyopath* OR coronar* OR myocard*) NEAR/3 (ischem* OR ischaem* OR anoxia OR hypoxia)) OR (coronary NEAR/3 (insufficien* OR occlus* OR disease* OR acute OR atherosclero* OR arteriosclero* OR sclero* OR cardiosclero* OR constrict* OR vasoconstrict* OR obstruct* OR stenosis* OR thrombo*)) OR angina* OR ((heart OR myocard* OR cardiac OR cardial) NEAR/3 infarct*) OR ((cerebrovascul* OR brain OR 'cerebral vascular' OR 'cerebro vascular') NEAR/3 (accident* OR lesion* OR attack OR ischem* OR ischaem* OR insult* OR insuffucien* OR arrest* OR apoplex*)) OR cva OR stroke OR (chronic AND (obstruct* NEAR/3 (lung* OR pulmonar* OR airway* OR bronch* OR respirat*))) OR ((lung* OR pulmonar* OR colon* OR colorect* OR breast* OR mamma*) NEAR/3 (neoplas* OR cancer* OR carcino* OR adenocarcino* OR metasta* OR sarcom*)) OR (chronic NEAR/3 (kidney* OR nephropathy* OR renal)) OR (('adult onset' OR 'type 2' OR 'type ii' OR 'non-insulin dependent' OR 'noninsulin dependent' OR 'insulin independent') NEAR/3 diabet*) OR ((cervix OR cervical) NEAR/3 (cancer* OR neoplas* OR tumo* OR carcinom* OR malign*))):ab,ti) AND (adult/exp) AND ('randomized controlled trial'/exp OR 'cohort analysis'/de OR 'case control study'/exp OR 'cross-sectional study'/de OR 'systematic review'/de OR 'meta analysis'/de OR ecology/exp OR 'ecosystem health'/exp OR 'ecosystem monitoring'/exp OR model/exp OR ((random* NEAR/3 (trial* OR control*)) OR rct* OR cohort* OR 'case control' OR 'cross-sectional' OR (systematic* NEAR/3 review*) OR metaanaly* OR (meta NEXT/1 analy*) OR ecolog* OR ecosystem* OR model*):ab,ti) NOT ([animals]/lim NOT [humans]/lim) NOT ([Conference Abstract]/lim OR [Conference Paper]/lim OR [Letter]/lim OR [Note]/lim OR [Conference Review]/lim OR [Editorial]/lim OR [Erratum]/lim)

AND ((('cost of living'/de OR budget/de OR 'financial deficit'/exp OR income/de OR 'health care cost'/de OR 'hospitalization cost'/de OR insurance/exp OR 'cost of illness'/de OR socioeconomics/exp OR (((cost* OR econom* OR expen*) NEAR/6 (living OR individu* OR famil* OR personal* OR patient* OR illness* OR direct* OR indirect*)) OR budget* OR deficit* OR debt* OR income OR insurance* OR socioeconom* OR pover* OR impover* OR poor OR wealth):ab,ti) AND (family/exp OR home/de OR household/de OR (famil* OR home OR household* OR personal):ab,ti)) OR 'caregiver burden'/de OR (microeconom* OR (micro NEXT/1 econom*) OR 'Out of pocket' OR 'Willingness to pay' OR (catastroph* NEAR/3 (spend* OR expend*)) OR 'Poverty line' OR (Value* NEXT/2 'statistical life')):ab,ti)

Appendix 2.
Newcastle Ottawa Quality Assessment Scale, cross-sectional and descriptive studies.

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is definition of NCDs adequate?
- a) Yes, according to a clear and widely used definition *
- b) Yes, e.g. record linkage or based on self-reports
- c) No description

2) Representativeness of the cases
- a) Consecutive or obviously representative series of cases *
- b) Excluded cases are random *
- c) No description of the excluded cases or potential for selection biases or not stated

3) Comparison with a reference group
- a) The results are compared with a reference from community or with the status of the cases prior to the disease *
- b) The results are compared with the results from other patients
- c) No description/no comparison available

4) Definition of reference
- a) Individuals with no NCD or sample from general population or the same individuals before NCD suffering*
- b) Non community comparator is described
- c) No description of source

Comparability

1) Comparability of the results on the basis of the design or analysis
- a) The results are described in age and sex sub groups (sex is not applicable for female diseases) *
- b) The results are additionally adjusted for/described in different socioeconomic factors or disease related confounders*

Exposure (costs, productivity, households)

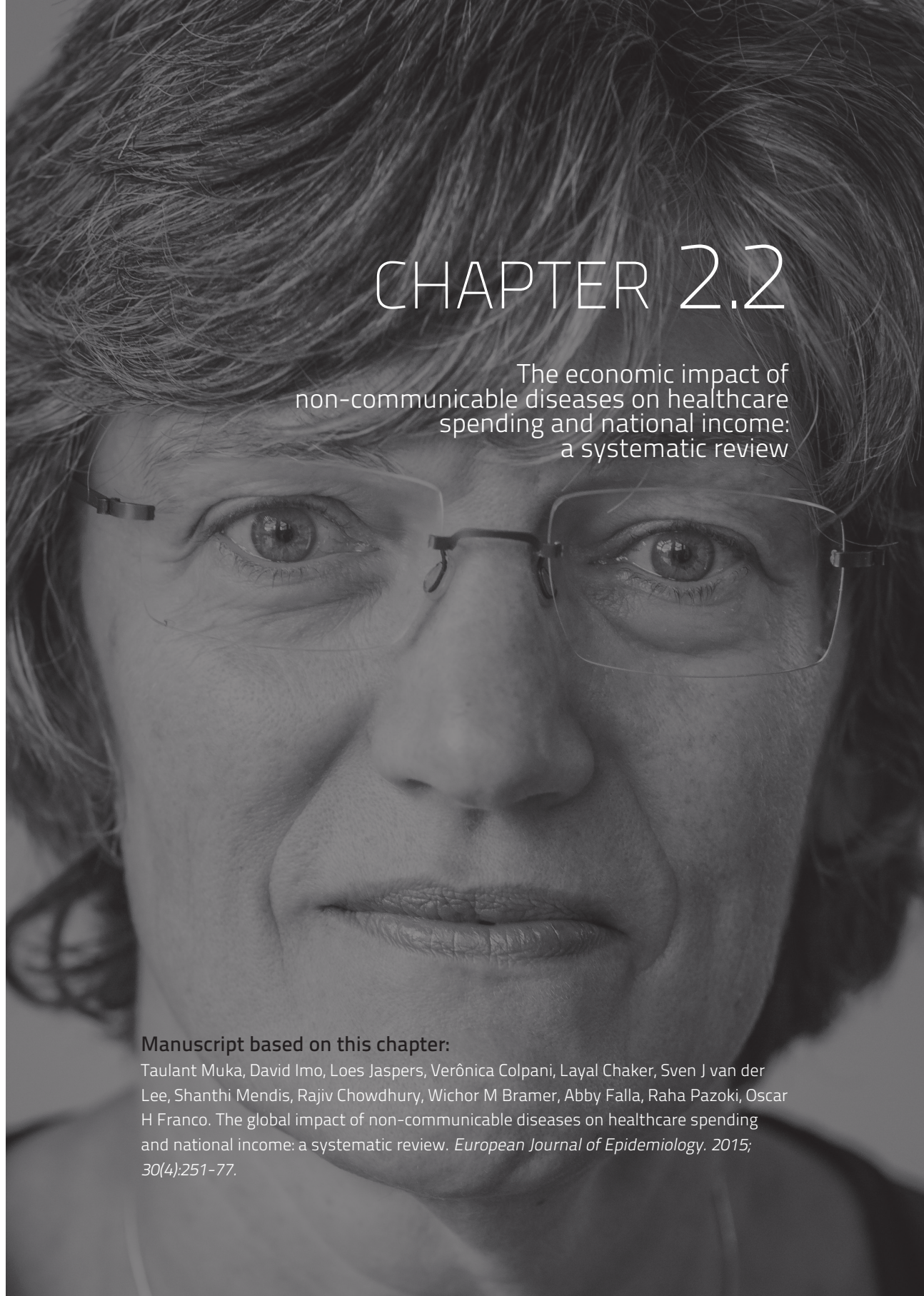
1) Ascertainment of exposure
- a) Secure record (e.g. surgical records, hospital records, and administrative records, national…) *
- b) Structured interview where blind to case/control status *
- c) Interview not blinded to case/control status
- d) Written self-report or medical record only
- e) No description

2) Same method of ascertainment for NCDs and comparators

a) Yes *
b) No
c) No comparator group exist

3) Non-response rate

a) All participants included or same rate for both groups or respondents and non-respondents have the same characteristics*
b) Non respondents described
c) Rate different and no designation
d) Response rate not described



CHAPTER 2.2

The economic impact of non-communicable diseases on healthcare spending and national income: a systematic review

Manuscript based on this chapter:

Taulant Muka, David Imo, Loes Jaspers, Verônica Colpani, Layal Chaker, Sven J van der Lee, Shanthi Mendis, Rajiv Chowdhury, Wichor M Bramer, Abby Falla, Raha Pazoki, Oscar H Franco. The global impact of non-communicable diseases on healthcare spending and national income: a systematic review. *European Journal of Epidemiology. 2015; 30(4):251-77.*

ABSTRACT

Background:

The impact of non-communicable diseases (NCDs) in populations extends beyond ill-health and mortality with large financial consequences.

Objective:

To systematically review and meta-analyze studies evaluating the impact of NCDs (including coronary heart disease, stroke, type 2 diabetes mellitus, cancer (lung, colon, cervical and breast), chronic obstructive pulmonary disease (COPD) and chronic kidney disease) at the macro-economic level: healthcare spending and national income.

Data sources:

Medical databases (Medline, Embase and Google Scholar) up to January 20th 2014. For further identification of suitable studies, we searched reference lists of included studies and contacted experts in the field.

Study selection:

We included randomized controlled trials, systematic reviews, cohorts, case-control, cross-sectional, modeling and ecological studies carried out in adults assessing the economic consequences of NCDs on healthcare spending and national income without language restrictions. All abstracts and full text selection was done by two independent reviewers. Any disagreements were resolved through consensus or consultation of a third reviewer.

Data extraction:

Data were extracted by two independent reviewers using a pre-designed data collection form.

Main outcome measures:

Studies evaluating the impact of at least one of the selected NCDs on at least one of the following outcome measures: healthcare expenditure, national income, hospital spending, gross domestic product (GDP), gross national product (GNP), net national income (NNI), adjusted national income (NNI), total costs, direct costs, indirect costs, inpatient costs, outpatient costs, per capita healthcare spending, aggregate economic outcome, capital loss in production levels in a country, economic growth, GDP per capita (per capita income), percentage change in GDP, intensive growth, extensive growth, employment, direct governmental expenditure and non-governmental expenditure.

Results:

From 4364 references, 153 studies met our inclusion criteria. Most of the studies were focused on healthcare related costs of NCDs. 30 studies reported the economic impact of NCDs on healthcare budgets and 13 on national income. Healthcare expenditure for cardiovascular disease (12-16.5%) was the highest; other NCDs ranged between 0.7%-7.4%. NCD-related health costs vary across the countries, regions, and according to type of NCD. Additionally, there is an increase in costs with increased severity and years lived with the disease. Low- and middle-income countries were the focus of just 16 papers, which suggests an information shortage concerning the true economic burden of NCDs in these countries.

Conclusions:

NCDs pose a significant financial burden on healthcare budgets and nations' welfare, which is likely to increase over time. However further work is required to standardize more consistently the methods available to assess the economic impact of NCDs and to involve (hitherto under-addressed) LMI populations across the globe.

Keywords:

non-communicable diseases, national income, health expenditure, systematic review

INTRODUCTION

Due to lifestyle and environmental change, healthcare improvements and improved potential to survive until old age, non-communicable diseases (NCDs) (including coronary heart disease (CHD), stroke, chronic obstructive pulmonary disease (COPD), cancer, type 2 diabetes mellitus (DM) and chronic kidney disease (CKD) are currently the leading cause of adult death and disability worldwide.[1] The global burden of NCDs is expected to rise further as a result of an increasing global population and demographic shifts, especially increases in the older population. Indeed, the global population above the age of 60, the age group most affected by NCDs, is expected to double between 2000 and 2050.[2]

Most NCDs are chronic conditions that require expensive treatment regimens and prolonged individual care by increasingly specialized healthcare services. NCDs also detrimentally impact on national income, socio-economic development and economic growth[3] through productivity losses, prolonged disability and increases in health and social care expenditure. Historically, high-income countries (HIC) experience the greatest economic consequences of NCDs. Yet, as a result of economic growth, epidemiological transition, ageing populations and healthcare system development, many low- and middle-income countries (LMIC) are now also experiencing a greater impact of NCDs. LMICs also suffer a substantial burden of NCD-related risk factors such as tobacco use, heavy alcohol consumption or unhealthy diet among their impoverished population groups.[4] However, policy programs that respond to the increasing burden of NCDs in many LMIC remain limited.[5] To date, however, little work has been done to systematically appraise the current evidence on the economic burden of NCDs globally. Exploring the studies that investigate the impact of NCDs on healthcare expenditure and national income can help shape future healthcare plans and strategies by better informing policy makers and healthcare planners about the emerging costs of NCDs.

We aimed to systematically review the literature evaluating the financial burden of six major NCDs (CHD, stroke, cancer (lung, colon, cervical and breast), COPD, DM and CKD) at the macro-economic level in order to quantify: (i,) the costs related to NCDs (direct, indirect, aggregate, over time and by disease severity); (ii) the per capita healthcare expenditure on NCDs; and (iii) national economic loss due to NCDs; and (iv) the overall aggregate economic impact of the NCDs on national income and healthcare spending.

METHODS

Search strategy and inclusion criteria

We conducted a systematic search of electronic medical databases (Medline, Embase and Google Scholar) until November 6th 2014 (date last searched) to retrieve scientific articles assessing the consequences of NCDs at the macro-economic level specifically

the impact on national income and healthcare expenditure (including: health expenditure, national income, hospital spending, gross domestic product (GDP), gross national product (GNP), net national income (NNI), adjusted national income (NNI), healthcare costs, direct costs, indirect costs, per capita healthcare spending, medical costs, non-medical costs, aggregate economic outcome, capital loss in production levels in a country, economic growth, percent rate of increase in GDP, GDP per capita (per capita income), intensive growth, extensive growth, employment, direct governmental expenditure and non-governmental expenditure) (see *Appendix 1* in the Supplement). The step-wise inclusion and exclusion procedure outlined in *Figure 1* was followed. Eligible study designs included randomized controlled trials (RCTs), cohort, case-control, cross-sectional, systematic reviews, ecological studies and modeling studies. We included studies evaluating the impact of at least one NCDs selected (CHD, stroke, COPD, type 2 diabetes mellitus, cancer (lung, colon, breast, and cervical), and CKD) on at least one measure of the impact on national income and healthcare expenditure (as specified above). Only studies carried out in adults (>18 years old) were included and we specified no language or date restrictions.

Study selection

Two independent reviewers screened the abstracts retrieved by the search strategy and selected eligible studies. Any disagreements between the two reviewers were resolved through consensus or consultation of a third independent reviewer. The references of the retrieved studies were scanned to identify additional relevant publications that were missed by the initial search strategy. Authors of the included studies were contacted in order to identify additional publications.

Data extraction

A predesigned data collection form was prepared to extract the relevant information from the included full texts, including study design, WHO region, characteristics of the study participants, NCDs details and economic measures reported.

Quality evaluation

We used the Newcastle-Ottawa Scale (NOS) to evaluate the quality of cross-sectional, case-control and cohort studies included in this review.[6] NOS scale assesses the quality of the articles in three domains of selection, comparability and exposure. Within the selection category, four items are assessed and a maximum of one star can be awarded to each item. Two stars can be awarded to the one item within the comparability category. Finally, one star can be awarded to each of the four items in the exposure category. A score will be made by adding up the number of stars and thus, NOS scale can have a maximum of nine stars in total. We used this scale for quality assessment of case-control and cohort studies. For cross-sectional and descriptive studies we used an adapted version of NOS scale (see *Appendix 2* in the Supplement). No quality score was applied to the modeling studies.

Statistical analyses

Heterogeneity permitting, we sought to pool the results using a random effects meta-analysis model. If pooled, results were expressed as the pooled estimate and the corresponding 95% confidence intervals. All costs presented are converted in USD 2013.

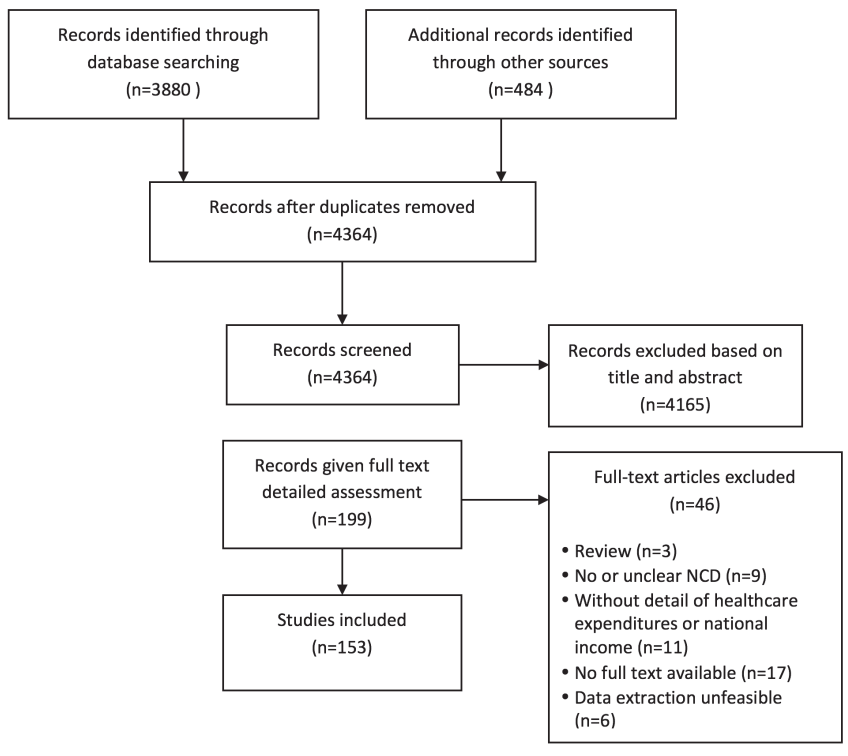
RESULTS

In total, we identified 4364 potentially relevant citations (*Figure 1*). Based on the title and abstracts, full texts of 199 articles were selected for detailed evaluation. Of those, 153 articles met our eligibility criteria and were therefore included in the analysis (*Table 1*).

General characteristics of the included studies

A wide geographical distribution was observed in the reviewed studies. The majority of the

Figure 1. Flowchart of studies for the global impact of non-communicable diseases on healthcare spending and national income.



studies (n=68) were from the American WHO region (mainly USA and Canada), 57 studies were from the European, 19 from the Western Pacific, two from the South-East Asian, three and from the African WHO region and the Eastern Mediterranean respectively, whereas two studies were conducted in multiple regions. The majority (n=137) of the reviewed studies were conducted in HIC, ten in upper middle-income countries, and five were conducted in low-income countries whereas one study included countries from the three income categories. Therefore, the GDP variation across the studies reviewed was narrow. The studies identified were mainly observational studies, having a retrospective or longitudinal design; 22 studies were modeling studies and only one study was an RCT. Medical records were the most frequently used method to select participants. In many cases, these medical records were linked to socio-economic databases to extract employment data. Adjustment for age, gender, ethnicity, co-morbidities/existing conditions, and geographic regions was usually applied.

Of the 153 studies included in this review, 40 studies focused on the economic impact of CHD and stroke (cardiovascular disease), 32 on COPD, five on CKD, 24 on DM, 45 on cancer and 7 studies provide evidence on economic impact of a combination of NCDs (*Table 1*). Most of the studies investigated the economic impact of NCDs among people aged 45 years and over.

Per patient global healthcare costs and non-healthcare costs of NCDs

Reported healthcare costs associated with NCDs varied across countries and regions, and across the type of NCDs. Reported annual direct costs of NCDs were the highest in the Americas, followed by European and Western Pacific regions; in the region of the Americas, the minimum and maximum mean reported annual total direct costs for CVD were 6668 USD[7] and 81096 USD[8], respectively, whereas the average annual direct costs for CVD varied from 1643[9] USD to 69440 USD[10], and from 3862 USD[11] to 5693 USD[12] for the European and Western Pacific regions, respectively (*Supplemental Table 1*). A detailed description on the variation of any type of costs of NCDs per world region is shown in *Supplemental Table 1*.

Direct costs

In 107 studies, mean annual total direct costs and mean directly attributable costs per NCDs patient (*Table 2A*) were estimated. Worldwide, of all the selected NCDs, cancer and CVD (with estimated costs up to 197772 USD[13] and 81096 USD[8], respectively) had the highest reported mean annual total direct costs, whereas DM had the lowest. Average CVD-related direct costs ranged from 1643 USD[9] in Poland to 81096 USD[8] in USA, with CHD having the lowest reported estimates and heart failure imposing the highest costs. Among cancers, the estimated mean annual total direct costs varied: from 4595 USD[14] to 82794 USD[15] for breast cancer; 4964 USD[16] to 161048 USD[15] for lung cancer and 220817 USD to 197722 USD[17] for colorectal cancer. Only one study from Singapore reported annual total direct costs for cervical cancer with an average estimate of 8049 USD[18]. COPD annual direct costs varied substantially, with Norway reporting the lowest direct

costs (431 USD[19]) and USA reporting the highest (34101 USD[20]). The lowest direct costs for CKD were observed in Germany with an average estimate of 5439 USD[21], whereas mean direct costs for CKD in USA were estimated to be up to 71824 USD[22]. DM average annual direct costs varied from 162 USD[23] in India to 15611 USD in USA[24].

Direct attributable costs for the NCDs were available from only 18 studies. The highest direct attributable costs were observed for cancer (up to 190032 USD[13]), followed by CKD (up to 33585 USD[25]), COPD (up to 22183 USD[24]), CVD (up to 21152 USD[24]) and finally, DM (up to 12246 USD[24]) with the lowest average estimates. Some articles reported inpatient and outpatient costs for NCDs (*Supplemental Table 2)*. These demonstrate that inpatient costs are the main source of direct costs for NCDs. Inpatient costs accounted for 47%-58% of total direct costs of COPD[26] and 63% of total direct costs for DM[27]. Hospital costs represent the main driver of stroke expenditure, accounting for 90%[28] of total direct costs. Hospitalization charges represented the greatest economic burden (55%)[29] for the management of colorectal cancer, followed by medical purchases (24%) and outpatient care (18%).

Indirect costs

18 studies estimated mean annual indirect costs (*Table 2B*). Mean annual estimated indirect costs for NCDs patients were highest for cancer and DM, with estimates up to 24740 USD[30] and 23418 USD[31], respectively. Mean annual indirect costs for breast cancer varied extensively, from 2109 USD[32] to 24740 USD[30]. The lowest indirect cost for COPD was reported in Japan, with an average estimate of 326 USD[33], and highest in USA (3393 USD[34]). Mean DM indirect annual costs were estimated at 104 USD in Serbia[35] compared to 7797 USD in China[27]. No study, however, reported annual indirect costs of colorectal cancer, lung cancer, cervical cancer or CKD.

Aggregate costs

Mean annual total costs of NCDs per patient were reported in 17 articles (*Table 2C)*. Cancer and stroke led the total costs with average estimates up to 105310 USD[30] and 44937 USD[31] respectively. The mean total cost per patient for breast cancer was estimated at 30000 USD in Belgium[36] and the USA[37], although the mean costs for metastatic breast cancer were three times higher (105310 USD[30]). For lung cancer, mean estimates varied from 4964 USD[16] in Australia to 50495 USD in USA[38] whereas colorectal cancer total costs were 52068 USD[38]. Mean COPD total costs were estimated around 1700 USD in the UK and Japan[33] but exceeded the value of 15500 USD in Denmark[39]. DM total costs were estimated at an average of 12920 USD in Sweden[40] whereas estimated mean total costs in Serbia were 1005 USD[41]. No study reported total costs for cervical cancer or CKD.

Costs of NCDs over time

There was an increase in healthcare costs associated with NCDs over time. One study showed that, despite a 19% decline in the hospitalization rate for CHD (acute myocardial infarction) in USA, overall healthcare expenditure per patient increased by 17% from 1998 to 2008 (absolute difference of 6595 USD) and use of outpatient services increased by 65% (absolute difference, 1000 USD)[42] and similarly for heart failure[43]. The average treatment cost of colorectal cancer patients in USA increased by 73% from 2005 to 2009[44], mainly driven by the use of new regimens, higher chances of surgery, and radiation. In USA, COPD-related healthcare costs increased by 5-6% annually[45]. Further, a 29% increase in medical treatment costs for diabetic patients was observed from 1999 to 2001 in Israel (absolute difference, 771 USD)[46].

Costs according to disease severity and comorbidity

Overall healthcare costs secondary to NCDs increased with the severity of the disease, years lived with the condition and co-morbidity[9 36 47-57]. Patients with severe stroke had almost a 40% greater increase in costs compared to mild stroke patients[47]. Among cancer patients, given the same stage of diagnosis, those with one, two or three co-morbidities experienced increased costs of 3737 USD, 4188 USD and 10442 USD respectively[58]. Costs for a diabetic patient tripled between the first and seventh year[59] after diagnosis. An increase in treatment costs of breast cancer by stage was reported, with approximately 52% higher treatment costs for stage II as compared to stage 0[57]. Similarly, a 29859 USD increase was seen with cancer progression from stage I to stage IV[29]. Patients with co-existence of COPD and CVD had 135% higher annual care costs compared with patients without CVD, whereas COPD related total costs were 38% higher[56]. Some studies reported lifetime healthcare costs of NCDs (initial, continuing and terminal care), demonstrating that initial and terminal care are the most costly.[13 15 60-62].

Global healthcare expenditure on NCDs

Among the reviewed studies, 30 reported healthcare expenditure attributable to specific NCDs (*Table 3A*). CVD accounted for 12% of all healthcare expenditure in the European Union (EU)[63]. CHD healthcare-related costs accounted for 14.2-16.5% of the annual healthcare budget in the American region. In contrast, in the EU, mean healthcare expenditure on CHD was 2.6%; within the EU, Malta has the lowest share (0.6%) and Slovakia the highest (5.9%)[63]. CKD and cancer accounted for 3.2% and 3.4%, of healthcare expenditure respectively[25 64]. In the USA, 1.2% of the healthcare budget was spent exclusively on the treatment of breast cancer[25]. The proportion of national healthcare-related expenditure for COPD ranged from 0.7% in Norway[19], 1-3% in the Netherlands[65] and up to 3.8% in Canada[64]. Again in Canada, 3.8% of healthcare expenditure is attributable to DM[64] whereas in the European Union, DM-related healthcare expenditure was an estimated 7.4%[66] (the Netherlands having the lowest share (1.6%), and Spain the highest)[67].

In absolute terms, annual CVD hospital costs in the USA reached an estimated 400 billion USD in 2008, doubling the 195 billion USD in 1995[68,69]. In USA, CHD-related hospital costs were estimated at 59.1 million USD in 1995 whereas the CVD-related hospital costs were 130 USD billion in 2010[70]. In the EU, CVD-related hospital costs were estimated at 151 billion USD in 2003, with CHD accounting for 32.9 billion USD[63]. In Australia, annual hospital costs due to CVD were estimated at 164 million USD in 1997[71]. In France and

Hungary the annual estimated colorectal cancer health related costs were 565 million USD and 43 million USD respectively[72,73]. In Iran, the minimum annual healthcare-related cost for colorectal cancer was estimated at 39 million USD for the period between 2005 and 2010[74]. For cervical cancer, the estimated costs were 1.83 million USD in Singapore[18,] 18.2 million USD in Spain[75], and 12.98 million USD in Malaysia[76]. The estimated total healthcare costs in the USA for lung, colorectal, cervical and breast cancer combined were 5.2 billion[77]. In USA, health-related costs for COPD and CKD in 2005 were an estimated 9.2 billion USD[24]. COPD costs accounted for 232 million USD in Iceland[19] whereas both COPD and DM accounted for 162 million USD in Australia[78]. DM hospital-related costs varied from 9.7 billion USA in the African Region[79], to 41.1 billion USD67 in Europe and to 160 billion USD in USA[80].

A data series of hospital expenditure on CVD was only available in the USA. This showed a two fold increase in healthcare share from 1995 to 2008, with estimated health costs of 195 billion USD in 1995 to 400 billion USD in 2008[68 69]. An increase in healthcare expenditure was also seen for colorectal cancer in Brazil, from 18.54 million USD in 1996 to 37.64 million USD in 2008[81]. Yoon, J.J et al showed a sharp increase in healthcare spending on most chronic diseases from 2000 to 2008, with CKD having the highest increase by more than 1.62 billion USD[82].

Impact of NCDs on national income

In general, NCDs have a large impact on national income mainly due to loss of productivity as a result of absenteeism and inability to work in 13 studies (*Table 3B*). There was a 463 billion USD increase in economic loss in USA due to CVD for the period 1993-2008[68]. In the EU, estimated economic loss in 2003 was 92.9 billion USD for CVD, of which CHD accounted for 31.84 billion USD. Estimated loss in national income from CHD-related productivity loss in 1996 was 71 billion USD in Germany[83]. Economic loss from stroke in 1997 was 51.7 million USD in Australia[84] whereas CHD-related productivity loss was 2.2 billion USD in 2004[85]. Worldwide, economic loss from colorectal, lung, breast and cervical cancer at 2009 year were 13.7, 8.2, 1.7 and 8.4 billion USD respectively[86]. In Malaysia, estimated income losses from cervical cancer-related productivity loss were 4.1 million USD. In the Netherlands, estimated losses in national income from COPD were 388 million USD[76 87]. National income losses from DM were estimated at 20.8 billion in the African region in 2000 and at 65.2 billion in 2007 in USA[79 88].

Combined impact of NCDs on national income and healthcare expenditure

19 studies reported the impact of NCDs on both healthcare expenditure and national income (*Table 3C*). The total estimated cost of CVD in Germany in 1999 was 108.9 billion USD whereas for the entire EU, the estimate was 244.3 billion USD for the year 2003, with CHD accounting for 26% of this cost[63 83]. Stroke costs were up to 1.3 billion USD in Australia, 3.47 billion USD in Canada and 72.4 billion USD in USA[71 89 90]. Worldwide, colorectal, lung, breast and cervical cancer made up 41% (127.8 billion USD) of the 310.15 billion USD aggregate cost of new cancer cases in 2009, with lung cancer posing the highest economic

burden (57.4 billion USD)[86]. In the USA, colorectal cancer and lung cancer total costs were 2.5 billion USD[38] each whereas in France, the total colorectal cancer costs were estimated at 1.24 billion USD[72]. In Malaysia, the total estimated cervical cancer costs were 17.1 million[76]. Total COPD costs varied from 133.7 million in the Netherlands to 1.1 billion USD in Sweden and 9.1 billion USD in Japan[33 49 87]. Total estimated costs of DM increased from 142.5 billion USD in 1997, to 171 billion USD in 2002 and to 195.5 billion USD in 2007[80 88 91]. DM imposed 30.4 billion USD in costs on the African region and 46.7 billion USD in costs in China[27 79].

DISCUSSION

This systematic review summarizes 153 studies published worldwide that investigate the impact of six major NCDs (CHD, stroke, COPD, major cancers, type 2 diabetes and CKD) at the macro-economic level (i.e. health-related costs, healthcare budgets and national income). The studies suggest a steady global increase in healthcare expenditure on NCDs over the years. Additionally, NCDs undermine national economic development, with estimated losses in national income in excess of 600 billion USD.[68]

In most countries, the highest expenditure was attributable to CVD. Between 12% and 16.5% of the overall healthcare budget is spent on this one condition alone; the proportion spent on the other NCDs ranges from 0.7% to 7.4%. In the USA and Brazil hospital expenditure on major NCDs doubled in a decade to an estimated 200 billion USD. An increasing share of healthcare expenditure on major NCDs has been reported previously and especially so in Germany where an increase from 27-51% of total health expenditure was reported.[92] Similarly, in the USA, CHD-related healthcare costs were five times higher in 2008 than in 1996. Yet, little is known about what drives current and future NCDs-related healthcare costs. Interesting insights come from Australia; these show that the introduction of new technologies and changes in treatment practices (volume of treatment services) are more likely to drive healthcare costs as compared to ageing or other factors.[93] In the overall projected increase in health expenditure in Australia up to 2032, volume of treatment services had the largest contribution (AUD 81.3 billion), followed by population ageing (AUD 37.8 billion) and population growth (AUD 34.4 billion). Also, Aaron, H et al. in a summary of the current evidence reported that most of the anticipated increase in total health care spending in USA is attributed to growth of age-specific health care spending and some will be caused by population ageing.[94] However, although health care spending at a time point in time may be influenced by ageing and in particular by the remaining life expectancy (and increases in longevity), there is limited data available projecting how the health care spending curve will evolve as life expectancy increases[94]. More research is warranted in this respect.

Further, NCDs have a large impact on national income, with estimated losses ranging

from 4.1 million USD due to cervical cancer in Malaysia, to 71 billion USD in Germany and 600 billion USD in the USA due to CHD. Large-scale productivity losses mainly due to absenteeism and an inability to work, caused by the debilitating physical and mental impact of NCDs, have a direct detrimental impact on national income. A 2005 WHO report indicated that estimated losses in national income due to CVD, stroke and diabetes were 3 billion USD in Brazil, 9 billion USD in India, 11 billion USD in Russia and 18 billion USD in China.[95] Bradley et al. demonstrated that, with the same level of colorectal cancer risk factors in USA, estimated economic losses due to colorectal cancer would raise from 24.2 billion USD in 2011 to 339 billion USD in 2020.[96] A macro-economic simulation presented at the World Economic Forum in 2011 showed that over the next two decades, NCDs would lead to a staggering 47 USD trillion cumulative output losses globally, representing 75% of global GDP in 2010.[97]

While the current study is the most detailed systematic review on the topic, it is limited by the fact that the evidence on economic burden of NCDs in LMIC is generally scarce. Most of the evidence in this review originates from high-income countries. Limited research capacity, inadequate financial investment, healthcare system development, a lack of electronic health records, and language restrictions may contribute to this shortage.[98] Using a systematic search in Pubmed and Embase, 14 review articles[99 100-112] (including four systematic reviews[99-101 106]) evaluating the economic impact of different NCDs on healthcare expenditure were found. The majority of these reviews were not performed systematically and previous systematic reviews [99-101 106] have been published on the costs of specific NCDs. Valtorta and colleagues[100] investigated the financial consequences of cancers, stroke, and heart failure but did not include diabetes, CVD, COPD, or CKD. Yabroff and colleagues[99] used only MEDLINE, were focused on recent articles in English language, and tackled only colorectal cancer.

Findings of this systematic review generally concur with and further extend the previous reviews. This systematic review evaluates economic consequences of six major NCDs using a global perspective in a single comprehensive investigation. Two reviewers, working in tandem, screened and selected the studies, while references of the included studies were additionally screened for any missing evidence. This approach ensured that we included most of the relevant articles in our review. Similar to previous reviews, however, we found substantial methodological limitations. Age range or stage of disease at diagnosis or other patients characteristics that may influence care and costs, were frequently not reported. Furthermore, many studies did not clearly state the method used to estimate costs and among the others, different approaches were used to calculate the same type of costs; e.g. direct attributable costs to diabetes were calculated by 1) including the direct costs of the events undergoing investigation; 2) comparing the cost of diabetes patients to those with no diabetes history; or 3) comparing previous resource use to resources use after the event. It may be argued that the studies using the first approach may not include all the costs associated with the disease. For example,

diabetes patients are more likely to have fractures than those without diabetes.[113] Moreover, several methodological concerns of the studies reviewed were observed, related to sample selection and representativeness, case definition, the nature of costs included (e.g. all-cause or event-related) and the analysis costs of data over time. Also, there are differences among countries with regard to health care/welfare system which may partly explain the large variation of health care spending across countries and world regions. In many countries, private spending accounts for three quarters of national health expenditure whereas in some others, there is a large burden of health care into the public purse. [114 115] Although, it would be of interest to compare health care spending and the impact of NCDs on national income based on the organization of health care/ welfare system, this becomes challenging because of continuing pattern changes and shifts in health care/ welfare system in past several decades.[115] Hence, comparisons across studies were difficult and a meaningful quantitative pooling of the existing data remains unfeasible. Therefore, future studies, especially those involving economic burden assessment using a standardized approach and based in LMI settings, are warranted.

In spite of data limitations, the estimates reported here show that NCDs pose a significant financial burden on healthcare budgets and nations' welfare that is likely to increase over time. Further work is necessary to standardize the methods to consistently assess the economic impact of NCDs worldwide and to involve hitherto under-addressed LMI populations across the globe.

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Disclosures

With regard to potential conflicts of interest, there is nothing to disclose.

Supplemental material

Supplemental material related to this article can be found online at *http://link.springer.com/article/10.1007%2Fs10654-014-9984-2.*

Table 1. General characteristics of the studies included in this review.

Lead author	Period of surveillance	Location	WHO region	Study design	Number in analysis	Gender	Reported NCD	Quality score[a]
Abudagga, A; et al.[116] 2013	2011-2012	USA	AMR	Cohort	17382	Both	COPD	7
Ademi, Z; et al. [11] 2013	2004-2006	Australia	WPR	Cohort	2873	Both	CVD	8
Aljunid, S; et al.[76] 2010	2007-2008	Malaysia	WPR	Modeling	444	Female	Cervical cancer	NA
Anis, AH; et al.[7] 2000	1994-1995	Canada	AMR	Modeling	352	Both	COPD, CVD	NA
Baker, MS; et al.[15] 1991	1974-1981	USA	AMR	Longitudinal	125831	Both	Lung & breast cancer	6
Bakerly, N; et al.[117] 2009	2003-2004	UK	EUR	Cohort	225	Both	COPD	4
Ballesta, M; et al.[118] 2006	1999	Spain	EUR	Descriptive observational	517	Both	DM	5
Baumeister, SE; et al.[21] 2009	1994-2005	Germany	EUR	Combined	4856	Both	CKD	6
Beaulieu, N; et al.[86] 2009	2009	Worldwide	NA	Modeling	NA	Both	Lung, colorectal, cervical & breast cancer	NA
Biorac, N; et al.[41] 2009	2007	Serbia	EUR	Cohort	99	Both	DM	2
Blanchette, CM; et al.[50] 2008	2004	USA	AMR	Cohort	6243	Both	COPD	7
Blanchette, CM; et al.119 2012	1987-2007	USA	AMR	Cross-sectional	644	Both	COPD	7
Bonastre, J; et al.[120] 2012	1998-2008	France	EUR	Cohort	290	Female	Breast cancer	8
Boncz, I; et al.[73] 2010	2001	Hungary	EUR	Survey	NA	Both	Colorectal, cervical & breast cancer	5

Table 1. Continued

Lead author	Period of surveillance	Location	WHO region	Study design	Number in analysis	Gender	Reported NCD	Quality score[a]
Bottacchi, E; et al.[28] 2012	2004-2007	Italy	EUR	Cost of illness (cohort)	800	Both	Stroke	6
Bouvier, V; et al.[121] 2003	1997-1998	France	EUR	Survey	142	Both	Colorectal cancer	6
Broekx, S; et al.[36] 2011	1997-2004	Belgium	EUR	Cost of illness (cross sectional)	20439	Female	Breast cancer	3
Brown, ML; et al.[122] 1999	1990-1994	USA	AMR	Modeling	NA	Both	Colorectal cancer	NA
Caro, JJ; et al.[123] 2006	1990-1995	France	EUR	Cohort	18704	Both	Stroke	6
Chang, S; et al.[124] 2004	1998-2000	USA	AMR	Retrospective cohort	2858	Both	Lung & colorectal cancer	9
Chirikos, TN; et al.[125] 2008	1991-1999	USA	AMR	Cohort	80421	Both	Lung cancer	7
Chittleboroug, CR; et al.[78] 2009	1997-2002	Australia	WPR	Cross-sectional	2352	Both	COPD	7
Chodick, G; et al.[46] 2005	1999-2001	Israel	EUR	Cohort	24632	Both	DM	7
Chouaid, C; et al.[126] 2004	1998-1999	France	EUR	Modeling	428	Both	Lung cancer	NA
Christensen, MC; Munro, V;[127] 2008	2004-2005	UK	EUR	Cohort	1016	Both	Stroke	5
Claesson, L; et al.[47] 2000	1993-1994	Sweden	EUR	RCT	249	Both	Stroke	8
Clerc, L; et al.[29] 2008	2004-2005	France	EUR	Cohort	384	Both	Colorectal cancer	4
Cocquyt, V; et al.[14] 2003	1997-1998	Belgium	EUR	Modeling	118	Female	Breast cancer	NA
Costantino, ME; et al.[128] 2014	2008-2009	USA	AMR	Retrospective Cohort	389550	Both	DM	6

Table 1. Continued

Lead author	Period of surveillance	Location	WHO region	Study design	Number in analysis	Gender	Reported NCD	Quality score[a]
Corrao, G; et al.[129] 2014	2011	Italy	EUR	Cohort	26949	Both	Heart Failure	7
Dahlberg, L; et al.[130] 2009	2005-2006	Sweden	EUR	Cohort	53	Female	Breast cancer	6
Dalal, AA; et al.[45] 2011	2006-2009	USA	AMR	Cohort	42166	Both	COPD	4
Dalal, AA; et al.[131] 2011	2003-2008	USA	AMR	Cohort	4594	Both	COPD	4
Darkow, T; et al.[34] 2007	2001-2004	USA	AMR	Cohort	1349	Both	COPD	6
Davari, M; et al.[74] 2012	2005-2010	Iran	EMR	Cross-sectional	435	Both	Colorectal cancer	2
Degli Esposti, L; et al.[132] 2013	2009	Italy	EUR	Retrospective	21586	Both	DM	5
Dewey, HM; et al.[84] 2001	1997	Australia	WPR	Cost of illness	275	Both	Stroke	4
Dewey, HM; et al.[71] 2003	1997	Australia	WPR	Cost of illness	NA	NA	Stroke	4
Di Salvo, TG; et al.[133] 1996	1991-1992	USA	AMR	Cohort	292	Both	AMI	4
Domingo, C; et al.[134] 2006	NA	Spain	EUR	Cohort	124	Both	COPD	4
D'Souza, AO; et al.[135] 2014	2003-2007	USA	AMR	Retrospective	40884	Both	COPD	7
Elrayah-Eliadarous, H; et al.[136] 2010	2005	Sudan	EMR	Retrospective	822	NA	DM	3
Fernandez De Bobadilla, J; et al.[137] 2008	2006	Spain	EUR	Cohort	2858	Both	Stroke	4
Ferrandinda, G; et al.[138] 2010	2000-2007	Italy	EUR	Cohort	351	Female	Cervical cancer	6

Table 1. Continued

Lead author	Period of surveillance	Location	WHO region	Study design	Number in analysis	Gender	Reported NCD	Quality score[a]
Fireman, BH; et al.60 1997	1987-1991	USA	AMR	Survey	21977	Both	Lung, colorectal & breast cancer	8
Fletcher, MJ; et al.139 2009	2009	Cross-country	NA	Cross-sectional	2426	Both	COPD	
Gil, A; et al.75 2007	1999-2002	Spain	EUR	Retrospective	16604	Female	Cervical cancer	6
Gruber, EV; et al.140 2012	2009	Germany	EUR	Modeling	14000000	Female	Breast cancer	NA
Havlovicova, M; et al.141 2001	1997	Czech Republic	EUR	Cohort	224	Both	Stroke	6
Hilleman, DE; et al.51 2000	1993-1998	USA	AMR	Cohort (phamarco-economic analysis)	413	Both	COPD	4
Hodgson, TA; Cohen, AJ69 1999	1995	USA	AMR	Survey	NA	NA	CVD, CHD	NA
Hogan, P; et al.80 2003	2002	USA	AMR	Survey/ modeling	NA	Both	DM	NA
Hu, S; et al.142 2013	2010-2011	China	WPR	Cross-sectional	63	Both	Stroke	1
Hutchinson, A; et al.52 2010	2001-2002	Australia	WPR	Cohort	80	Both	COPD	6
Jansson, SA; et al.49 2002	1998-1999	Sweden	EUR	Cohort	212	Both	COPD	6
Jaworski, R; et al.9 2012	2005	Poland	EUR	Cohort	2593	Both	CAD	3
Jensen, MB; et al.53 2013	2004-2006	Denmark	EUR	Cohort	546	Both	COPD	7
Jonsson, B; et al.67 2002	1999	Europe	EUR	Retrospective	6996	Both	DM	3
Kabadi, GS; et al.143 2014	2005-2006	Tanzanie	AFR	Prospective	16	Both	Stroke	6

Table 1. Continued

Lead author	Period of surveillance	Location	WHO region	Study design	Number in analysis	Gender	Reported NCD	Quality score[a]
Kang, HY; et al.[144] 2011	2002-2004	Korea	SEAR	Modeling	NA	Both	Stroke	NA
Kang, S; et al.[16] 2012	2005-2008	Australia	WPR	Cohort	210	Both	Lung cancer	6
Kangas, T; et al.[145] 1996	1987-1989	Finland	EUR	Cross-sectional	NA	NA	DM	4
Kerrigan, M; et al.[146] 2005	1996-1998	USA	AMR	Case-control	346	Both	Colorectal cancer	9
Kim, TH; et al.[147] 2012	2005	Korea	WPR	Cohort	3125	Both	DM	3
Kirigia, JM; et al.[79] 2009	2000	Africa	AFR	Cost of illness	NA	Both	DM	NA
Klever-Deichert, G; et al.[83] 1999	1996	Germany	EUR	Modeling	NA	Both	CVD	NA
Kolominsky-Rabas, PL; et al.[148] 2006	1994-2003	Germany	EUR	Cost of illness	2458	Both	Stroke	5
Kumar, A; et al.[23] 2008	2005-2005	India	SEAR	Cross-sectional	819	Both	DM	2
Kuwabara, H; et al.[149] 2009	2003	Japan	WPR	Modeling	3490	Both	Breast cancer	NA
Laliberte, F; et al.[150] 2009	2000-2006	USA	AMR	Retrospective	91069	Both	CKD	7
Lamerato, L; et al.[151] 2006	1996-2002	USA	AMR	Cohort	1616	Female	Breast cancer	7
Lamping, DL; et al.[22] 2000	1995-1996	UK	EUR	Cohort	221	Both	CKD	6
Lang, K; et al.[62] 2009	1996-2002	USA	AMR	Cohort	56838	Both	Colorectal cancer	8
Le, C; et al.[27] 2013	2010-2011	China	WPR	Cross-sectional survey	9396	Both	DM	5
Leal, J; et al.[63] 2006	2003	Europe	EUR	Cost of illness	NA	Both	CVD, CHD	4

Table 1. Continued

Lead author	Period of surveillance	Location	WHO region	Study design	Number in analysis	Gender	Reported NCD	Quality score[a]
Lee, H; et al.[152] 2002	1999-2000	Canada	AMR	Prospective	166	Both	CKD	4
Lee, HC; et al.[12] 2013	1996-2003	Taiwan	WPR	Cohort	2368	Both	Stroke	6
Legorreta, AP; et al.[57] 1996	1989	USA	AMR	Longitudinal	205	Female	Breast cancer	5
Leigh, JP; et al.[153] 2003	1999	USA	AMR	Modeling	NA	Both	Colorectal cancer, CVD, CKD	NA
Likosky, DS; et al.[42] 2013	1998-1999/2008	USA	AMR	Cross-sectional	317043	Both	AMI	5
Lokke, A; et al.[39] 2014	1998-2010	Denmark	EUR	Case-Control	263622	Both	COPD	7
Lopez-Batista, J; et al.[31] 2012	2004	Spain	EUR	Cross-sectional	448	Both	Stroke	5
Lou,P; et al.[154] 2012	2008-2009	China	WPR	Cross-sectional	8217	Both	COPD	2
Low, JJ; et al.[18] 2012	2008-2033	Singapore	WPR	Modeling	NA	Female	Cervical cancer	NA
Luo, Z; et al.[58] 2009	1996-2000	USA	AMR	Case-control	17945	Both	Colon cancer	6
Macafee, DA; et al.[17] 2009	1981-2002	UK	EUR	Retrospective	227	Both	Colorectal cancer	4
Mandelblatt, JS; et al.[155] 2006	2000	USA	AMR	Cohort	418	Female	COPD	7
Mapel, DW; et al.[156] 2000	1997	USA	AMR	Case-control	1522	Both	COPD	8
Martin, S; et al.[59] 2007	1995-2003	Germany	EUR	Cohort	3142	Both	DM	2
Marton, P; et al.[157] 2006	2001	USA	AMR	Retrospective-Cohort	49510	Both	COPD	8

Table 1. Continued

Lead author	Period of surveillance	Location	WHO region	Study design	Number in analysis	Gender	Reported NCD	Quality score[a]
Meen, P; et al.[158] 2012	2006-2009	Germany	EUR	Cohort	2255	Both	COPD	5
Menzin, J; et al. 2008	2001-2002	USA	AMR	Cohort	16321	Both	IHD	5
Menzin, J; et al.[159] 2008	2004	USA	AMR	Cohort	8370	Both	COPD	5
Miravitlles, M; et al.[160] 2001	1996-1997	Spain	EUR	Cohort	2414	Both	COPD	6
Miravitlles, M; et al.[54] 2003	1997-1998	Spain	EUR	Cohort	1510	Both	COPD	7
Mittman, N; et al.[89] 2012	2005-2009	Canada	AMR	Cohort	232	Both	Stroke	4
Mohd Nordin, NA; et al.[48] 2012	2005-2009	Malaysia	WPR	Cross-sectional	813	Both	Stroke	6
Morsanutto, A; et al.[161] 2006	2001-2002	Italy	EUR	Retrospective longitudinal	299	Both	DM	3
Nakamura, K; et al.[162] 2008	1990-2001	Japan	WPR	Cohort	4535	Both	DM	4
Nichols, GA; et al.[68] 2010	2000-2008	USA	AMR	Survey	12278	Both	CVD	NA
Nielsen, R; et al.[19] 2009	2003-2004	Iceland/Norway	EUR	Survey	1415	Both	COPD	6
Nielsen, R; et al.[163] 2011	2005-2006	Norway	EUR	Cohort	286	Both	COPD	6
Nishimura, S; Zaher, C;[33] 2004	1990-2002	Japan	WPR	Modeling	501	Both	COPD	NA
Norlund, A; et al.[40] 2001	1992-1993	Sweden	EUR	Cross-sectional	1677	Both	DM	4
O'Brien, BD; et al.[164] 2001	1989-1994	Canada	AMR	Survey	593	Both	Colorectal cancer	6
Odden, MC; et al.[70] 2011	NA	USA	AMR	Modeling	NA	Both	CHD	NA

Table 1. Continued

Lead author	Period of surveillance	Location	WHO region	Study design	Number in analysis	Gender	Reported NCD	Quality score[a]
Oglesby, AK; et al.[165] 2006	1989-2003	USA	AMR	Cohort	10780	Both	DM	6
Ohinmaa, A; et al.[64] 2006	2000-2001	Canada	AMR	Survey	2133413	Both	CVD, COPD, DM	4
Oliva, J; et al.[66] 2004	2002	Spain	EUR	Cost of illness	2010365	Both	DM	NA
Perera, PN; et al.[166] 2012	2006	USA	AMR	Retrospective	1254703	Both	COPD	6
Petersen, M; Amer Diabet, A[88] 2008	2007	USA	AMR	Survey/ Modeling	301736	Both	DM	NA
Ramsey, SD; et al.[167] 2003	1984-1994	USA	AMR	Survey	68145	Both	Colorectal cancer	6
Rao, S; et al.[168] 2004	1997-1999	USA	AMR	Cohort	397	Female	Breast cancer	6
Ray, GT; et al.[25] 2000	1995-1996	USA	AMR	Retrospective	2076303	NA	Lung, colon & breast cancer, CVD, IHD, COPD, DM	7
Ray, NF; et al.[91] 1998	1989-1995	USA	AMR	Survey/ Modeling	NA	Both	DM	NA
Riley, GF; et al.[61] 1995	1984-1990	USA	AMR	Retrospective	287013	Both	Lung, breast & colorectal cancer	7
Ringborg, A; et al.[169] 2008	2000-2004	Sweden	EUR	Cohort	37756	Both	DM	4
Rutten-van Molken, MPMH; et al.[65] 1999	1993	Netherlands	EUR	Modeling	NA	Both	COPD	NA
Sasser, AC; et al.[37] 2005	1998-2000	USA	AMR	Cohort	2265	Female	Breast cancer, CVD	8
Schneider, M; et al.[24] 2009	2001-2005	USA	AMR	Survey	1649574	Both	COPD, CKD, cancer, Heart failure, DM	NA

Table 1. Continued

Lead author	Period of surveillance	Location	WHO region	Study design	Number in analysis	Gender	Reported NCD	Quality score[a]
Seal, BS; et al.[44] 2013	2005-2009	USA	AMR	Longitudinal	5160	Both	Colon Cancer	7
Selke, B; et al.[72] 2003	1999	France	EUR	Cost of illness	69046	Both	Colorectal cancer	6
Sharafkhaneh, A; et al.[170] 2010	1997-2004	USA	AMR	Cohort	59906	Both	COPD	8
Simoni-Wastile, L; et al.[171] 2009	2003-2005	USA	AMR	Cohort	3037	Both	COPD	5
Simpson, AN; et al.[172] 2013	2004-2005	USA	AMR	Case-control	8928	Both	Stroke	7
Sloss, EM; et al.[173] 2004	1995-1998	USA	AMR	Cohort	3149	Both	Stroke	4
Smith, DH; et al.[174] 2004	1996-2001	USA	AMR	Cohort	13796	Both	CKD	8
Soekhlal, RR; et al.[175] 2013	2008-2012	Netherlands	EUR	Retrospective	25657	Both	AMI	6
Song, X; et al.[13] 2011	2004-2009	USA	AMR	Cohort	6675	Both	Colorectal cancer	6
Sorensen, SV; et al.[30] 2012	2000-2007	USA	AMR	Modeling	49674	Both	Breast cancer	NA
Spieler, JF; et al.[176] 2004	1997	France	EUR	Cohort	435	Both	Stroke	6
Taplin, SH; et al.[177] 1995	1990-1991	USA	AMR	Survey	6107	Both	Colorectal & breast cancer	5
Taylor, TN; et al.[90] 1996	1990-1993	USA	AMR	Modeling	NA	NA	Stroke	NA
Tiemann, O; et al.[178] 2008	2005	Europe	EUR	Cross-sectional	3942	Male	AMI	8
Torres, US; et al.[81] 2010	1996-2008	Brazil	AMR	Survey	297108	Both	Colorectal Cancer	6
Toure, K; et al.[179] 2005	1997	Senegal	AFR	Cross-sectional	383	Both	Stroke	NA

Table 1. Continued

Lead author	Period of surveillance	Location	WHO region	Study design	Number in analysis	Gender	Reported NCD	Quality score[a]
Trogdon, JG; et al.[180] 2007	2000-2003	USA	AMR	Cohort	125052	Both	Stroke	3
Tuck, J; et al.[181] 1989	1985-1986	UK	EUR	Cohort	85	NA	Colorectal cancer	NA
Tunceli, O; et al.[182] 2007	1999-2002	USA	AMR	Cohort	512468	Both	DM	8
Unroe, KT; et al.[8] 2011	2000-2007	USA	AMR	Cohort	229543	Both	Heart failure	7
Van Boven, JFM; et al.[87] 2013	2009	Netherlands	EUR	Cross-sectional	94158	Both	COPD	6
Wan, Y; et al.[32] 2013	2005-2009	USA	AMR	Cohort	278	Female	Breast cancer	7
Ward, A; et al.[10] 2005	1994-1998	Germany	EUR	Prospective	491	Both	Stroke	5
Warren, JL; et al.[38] 2008	1991-2002	USA	AMR	Survey	306709	Both	Lung, colorectal & breast cancer	4
Winter, Y; et al.[183] 2008	2003	Germany	EUR	Cohort	76	Both	Stroke	2
Wright, GE; et al.[184] 2007	1992-1996	USA	AMR	Cohort	6108	Both	Colorectal cancer	8
Yabroff, KR; et al.[77] 2008	1999-2003	USA	AMR	Survey	2342558	Both	Lung, colorectal, cervical & breast cancer	6
Yabroff, KR; et al.[185] 2009	1998-2002	USA	AMR	Cohort	6377	Both	Colorectal cancer	5
Yang, SC; et al.[186] 2013	1998–2010	Taiwan	WPR	Cohort	66535	Both	Lung cancer	6
Yoon, J; et al.[82] 2011	2000-2008	USA	AMR	Cohort	4892300	Both	CVD, CKD, COPD, Stroke	4
Zheng, H; et al.[85] 2010	2004	Australia	WPR	Modeling	NA	Both	CHD	NA
Zhuo, X; et al.[187] 2013	2009-2010	United Kingdom	EUR	Modeling	NA	Both	DM	NA
Zorowitz, R; et al.[188] 2009	2003-2006	USA	AMR	Cohort	3438	Both	Stroke	6

Table 1. Continued

[a] No quality score was applied to the modeling studies.
AFR=African Region, AMI=acute myocardial infarction, AMR=Region of the Americas, CAD=coronary artery disease, CHD=coronary heart disease, CKD=chronic kidney disease, COPD=chronic obstructive pulmonary disorder, CVD=cardiovascular disease, DM=diabetes mellitus, EMR=Eastern Mediterranean Region, EUR=European Region, IHD=ischemic heart disease, NA=not applicable, NCDs=non-communicable disease, RCT=randomized controlled trial, SEAR=South-East Asia Region, WPR=Western Pacific Region.

Table 2A. Results of the included studies investigating annual direct costs of NCDs.

Study	Type of outcome	Outcome specified as	Assessment type	Study design	Point estimate	Reported NCDs	Year	Country
Ademi, Z; et al. 2013	Direct costs	Patient/year	Mean	3862	5508	CVD	2006	Australia
Anis, AH; et al 2000	Direct costs	Patient/year	Mean	6668	391	CVD	1995	Canada
Di salvo, TG; et al. 1996	Direct costs	Patient/year	Mean	13907	NA	CVD	1992	USA
Nichols, GA; et al. 2010	Direct costs	Patient/year	Mean	20512	42247	CVD	2008	USA
Sasser, AC; et al. 2005	Direct costs	Patient/year	Mean	16313	NA	CVD	2000	USA
Corrao, G; et al. 2014	Direct costs	Patient/year	Mean	15328	NA	HF	2011	Italy
Ray, GT; et al. 2000	Direct attributable costs	Patient/year	Mean	10647	NA	HF	1996	USA
Ray, GT; et al. 2000	Direct costs	Patient/year	Mean	27015	NA	HF	1996	USA
Schneider, KM; et al. 2009	Direct attributable costs	Patient/year	Mean	21152	NA	HF	2005	USA
Schneider, KM; et al. 2009	Direct costs	Patient/year	Mean	24517	NA	HF	2005	USA
Unroe, KT; et al. 2011	Direct costs	Patient/year	Mean	81096	89336	HF	2007	USA
Bottachi, E; et al. 2012	Direct costs	Patient/year	Mean	9030	NA	Stroke	2007	Italy
Fernandez De Bodadilla, J; et al. 2008	Direct costs	Patient/year	Mean	4429	NA	Stroke	2006	Spain
Cleason, L; et al. 2000	Direct costs	Patient/year	Mean	39527	100233	Stroke	1994	Sweden
Hu, S; et al. 2013	Direct costs	Patient/year	Mean	4779	NA	Stroke	2011	China
Lee, HC; et al. 2013	Direct costs	Patient/year	Mean	5693	NA	Stroke	2003	Taiwan
Lopez-Batista, J; et al. 2012	Direct costs	Patient/year	Mean	21520	18535	Stroke	2004	Spain
Simpson, AN; et al. 2013	Direct costs	Patient/year	Mean	33698	29486	Stroke	2005	USA

Table 2A. Continued

Study	Type of outcome	Outcome specified as	Assessment type	Study design	Point estimate	Reported NCDs	Year	Country
Simpson, AN; et al. 2013	Direct attributable costs	Patient/year	Mean	11164	29486	Stroke	2005	USA
Sloss, EM; et al. 2004	Direct costs	Patient/year	Mean	39641	NA	Stroke	1998	USA
Spieler, JF; et al. 2004	Direct costs	Patient/year	Mean	32291	26290	Stroke	1997	France
Taylor, TN; et al. 1996	Direct costs	Patient/year	Mean	32467	NA	Stroke	1993	USA
Trogdon, JG; et al. 2007	Direct costs	Patient/year	Mean	7294	NA	Stroke	2003	USA
Winter, Y; et al. 2008	Direct costs	Patient/year	Mean	7386	9814	Stroke	2003	Germany
Yoon, J; et al. 2011	Direct costs (2000)	Patient/year	Mean	11251	NA	Stroke	2008	USA
Yoon, J; et al. 2011	Direct costs (2008)	Patient/year	Mean	8436	NA	Stroke	2008	USA
Ward, A; et al. 2005	Direct costs	Patient/year	Mean	69440	NA	Stroke	1994-1998	Germany
Zorowitz, R; et al. 2009	Direct costs	Patient/year	Mean	31969	NA	Stroke	2006	USA
Ray, GT; et al. 2000	Direct attributable costs	Patient/year	Mean	7669	NA	IHD	1996	USA
Ray, GT; et al. 2000	Direct costs	Patient/year	Mean	17776	NA	IHD	1996	USA
Menzin, J; et al. 2008	Direct costs	Patient/year	Mean	35005	NA	IHD	2002	USA
Jaworski, R; et al. 2012	Direct costs	Patient/year	Mean	1643	NA	CHD	2005	Poland
Likosky, DS; et al. 2013	Direct costs	Patient/year	Mean	40071	NA	AMI	1998-1999	USA
Likosky, DS; et al. 2013	Direct costs	Patient/year	Mean	46667	NA	AMI	2008	USA
Schneider, KM; et al. 2009	Direct attributable costs	Patient/year	Mean	15796	NA	Cancer	2005	USA
Schneider, KM; et al. 2009	Direct costs	Patient/year	Mean	19161	NA	Cancer	2005	USA
Baker, MS; et al. 1991	Direct costs	Patient/year	Mean	49032	NA	Breast cancer	1974-1981	USA

Table 2A. Continued

Study	Type of outcome	Outcome specified as	Assessment type	Study design	Point estimate	Reported NCDs	Year	Country
Baker, MS; et al. 1991	Lifetime attributable costs	Per patient	Mean	82794	NA	Breast cancer	1974-1981	USA
Broekx, S; et al. 2011	Direct attributable costs	Patient/year	Mean	2989	NA	Breast cancer	2004	Belgium
Cocquyt, V; et al. 2003	Direct costs	Patient/year	Mean	4595	NA	Breast cancer	1998	Belgium
Dahlberg, L; et al. 2009	Direct costs	Patient/year	Mean	60519	NA	Breast cancer	2006	Sweden
Fireman, BH; et al. 1997	Direct costs	Patient/year	Mean	11953	72	Breast cancer	1987-1991	USA
Fireman, BH; et al. 1997	Direct attributable costs	Per patient	Mean	58608	625	Breast cancer	1987-1991	USA
Gruber, EV; et al. 2012	Direct attributable costs	Patient/year	Mean	10208	NA	Breast cancer	2009	Germany
Lamerato, L; et al. 2006	Direct costs	Patient/year	Mean	58973	NA	Breast cancer (recurrence)	2002	USA
Legorreta, AP; et al. 1996	Direct costs	Patient/year	Mean	42514	NA	Breast cancer	1989	USA
Rao,S; et al. 2004	Direct attributable costs	Patient/year	Mean	31140	NA	Breast cancer	2004	USA
Rao,S; et al. 2004	Direct costs	Patient/year	Mean	32118	NA	Breast cancer	2004	USA
Ray, GT; et al. 2000	Direct attributable costs	Patient/year	Mean	5065	NA	Breast cancer	1996	USA

Table 2A. Continued

Study	Type of outcome	Outcome specified as	Assessment type	Study design	Point estimate	Reported NCDs	Year	Country
Ray, GT; et al. 2000	Direct costs	Patient/year	Mean	9899	NA	Breast cancer	1996	USA
Riley, GF; et al. 1995	Direct costs	Patient/year	Mean	22628	NA	Breast cancer	1984-1990	USA
Sasser, AC; et al. 2005	Direct costs	Patient/year	Mean	18843	NA	Breast cancer	2000	USA
Sorensen, SV; et al. 2012	Direct costs	Patient/year	Mean	80572	NA	Breast cancer	2007	USA
Yabroff, KR; et al. 2008	Direct attributable costs	Patient/year	Mean	17315	NA	Breast cancer	1999-2003	USA
Baker, MS; et al. 1991	Direct costs	Patient/year	Mean	161048	NA	Lung cancer	1974-1981	USA
Baker, MS; et al. 1991	Lifetime attributable costs	Per patient	Mean	28049	NA	Lung cancer	1974-1981	USA
Chang, S; et al. 2004	Direct costs	Patient/year	Mean	105876	54132	Lung cancer	1998-2000	USA
Chouaid, C; et al. 2004	Direct costs	Patient/year	Mean	22003	NA	Lung cancer	1999	France
Fireman, BH; et al. 1997	Direct costs	Patient/year	Mean	25128	253	Lung cancer	1987-1991	USA
Fireman, BH; et al. 1997	Direct attributable costs	Per patient	Mean	54972	653	Lung cancer	1987-1991	USA
Kang, S; et al. 2012	Direct costs	Patient/year	Mean	4964	NA	Lung cancer	2008	Australia
Ray, GT; et al. 2000	Direct attributable costs	Patient/year	Mean	12777	NA	Lung cancer	1996	USA
Ray, GT; et al. 2000	Direct costs	Patient/year	Mean	24099	NA	Lung cancer	1996	USA
Riley, GF; et al. 1995	Direct costs	Patient/year	Mean	32724	NA	Lung cancer	1984-1990	USA
Yabroff, KR; et al. 2008	Direct attributable costs	Patient/year	Mean	68658	NA	Lung cancer	1999-2003	USA

Table 2A. Continued

Study	Type of outcome	Outcome specified as	Assessment type	Study design	Point estimate	Reported NCDs	Year	Country
Bouvier, V; et al. 2003	Direct costs	Patient/year	Mean	26577	NA	Colorectal cancer	1997-1998	France
Brown, ML; et al. 1999	Direct attributable costs	Patient/year	Mean	13726	NA	Colorectal cancer	1994	USA
Brown, ML; et al. 1999	Direct costs	Patient/year	Mean	27722	NA	Colorectal cancer	1994	USA
Chang, S; et al. 2004	Direct costs	Patient/year	Mean	66036	26304	Colorectal cancer	1998-2000	USA
Clerc,L; et al. 2008	Direct costs	Patient/year	Mean	42688	NA	Colorectal cancer	2005	France
Fireman, BH; et al. 1997	Direct costs	Patient/year	Mean	18189	236	Colorectal cancer	1987-1991	USA
Fireman, BH; et al. 1997	Direct attributable costs	Per patient	Mean	74860	1364	Colorectal cancer	1987-1991	USA
Kerrigan, M; et al. 2005	Direct attributable costs	Patient/year	Mean	60535	NA	Colorectal cancer	1996-1998	USA
Macafee, DA; et al. 2009	Direct costs (for female)	Patient/year	Median	2208	NA	Colorectal cancer	1981-2002	UK
Macafee, DA; et al. 2009	Direct costs (for male)	Patient/year	Median	2856	NA	Colorectal cancer	1981-2002	UK
Luo,Z; et al. 2009	Direct attributable costs	Patient/year	Mean	39507	NA	Colorectal cancer	2000	USA
Seal, BD; et al. 2013	Direct costs	Patient/year	Mean	105754	92290	Colorectal cancer	2009	USA

Table 2A. Continued

Study	Type of outcome	Outcome specified as	Assessment type	Study design	Point estimate	Reported NCDs	Year	Country
Ray, GT; et al. 2000	Direct attributable costs	Patient/year	Mean	15588	NA	Colorectal cancer	1996	USA
Ray, GT; et al. 2000	Direct costs	Patient/year	Mean	22631	NA	Colorectal cancer	1996	USA
Ramsey, SD; et al. 2003	Direct costs	Patient/year	Mean	6697	NA	Colorectal cancer	1984-1994	USA
Ramsey, SD; et al. 2003	Direct attributable costs	Patient/year	Mean	2806	NA	Colorectal cancer	1984-1994	USA
Riley, GF; et al. 1995	Direct costs	Patient/year	Mean	35631	NA	Colorectal cancer	1984-1990	USA
Wright,GE; et al. 2007	Direct costs	Patient/year	Mean	39399	NA	Colorectal cancer	1996	USA
Yabroff, KR; et al. 2008	Direct attributable costs	Patient/year	Mean	28090	NA	Colorectal cancer	1999-2003	USA
Yabroff, KR; et al. 2009	Direct attributable costs	Patient/year	Mean	43611	NA	Colorectal cancer	2002	USA
Low, JJ; et al. 2012	Direct costs	Patient/year	Mean	8049	NA	Cervical cancer	2008-2033	Singapore
Yabroff, KR; et al. 2008	Direct attributable costs	Patient/year	Mean	22769	NA	Cervical cancer	1999-2003	USA
Song, X; et al. 2011	Direct attributable costs	Patient/year	Mean	197772	639672	Metastatic Colorectal cancer	2009	USA
Song, X; et al. 2011	Direct costs	Patient/year	Mean	190032	NA	Metastatic Colorectal cancer	2009	USA

Table 2A. Continued

Study	Type of outcome	Outcome specified as	Assessment type	Study design	Point estimate	Reported NCDs	Year	Country
Anis, AH; et al. 2000	Direct costs	Patient/year	Mean	1777	221	COPD	1994-1995	Canada
Miravitlles, M; et al. 2001	Direct costs	Patient/year	Mean	1869	NA	COPD	1996-1997	Spain
Blanchette, CM; et al. 2012	Direct costs	Patient/year	Mean	18305	NA	COPD	2007	USA
Blanchette, CM; et al. 2012	Direct costs	Patient/year	Mean	13266	NA	COPD	1987	USA
Blanchette, CM; et al. 2008	Direct costs	Patient/year	Mean	28966	45625	COPD	2004	USA
Chittleborough, CR; et al. 2009	Direct costs	Patient/year	Mean	551	551	COPD	1997-2002	Australia
Dalal, AA; et al. 2011	Direct costs	Patient/year	Mean	4856	NA	COPD	2006-2009	USA
Dalal, AA; et al. 2011	Direct costs	Patient/year	Mean	2574	NA	COPD	2003-2008	USA
Domingo, C; et al. 2006	Direct costs	Patient/year	Mean	1881	3828	COPD	2006	Spain
D'Souza, AO; et al. 2014	Direct costs	Patient/Year	Mean	19587	682	COPD	2003-2007	USA
D'Souza, AO; et al. 2014	Direct attributable costs	Patient/Year	Mean	2323	NA	COPD	2003-2007	USA
Hilleman, DE; et al. 2000	Direct costs	Patient/year	Median	6429	NA	COPD	1993-1998	USA
Hutchinson, A; et al. 2010	Direct costs	Patient/year	Median	6656	NA	COPD	2001-2002	Australia
Jansson, SA; et al. 2002	Direct costs	Patient/year	Mean	692	NA	COPD	1998-1999	UK
Nielsen, R; et al. 2011	Direct costs	Patient/year	Mean	13583.25	NA	COPD	2005-006	Norway
Jensen, MB; et al. 2013	Direct costs	Patient/year	Mean	4751	NA	COPD	2004-2006	Denmark
Lokke, A; et al. 2014	Direct costs	Patient/year	Mean	12321	NA	COPD	1998-2010	Denmark
Lokke, A; et al. 2014	Direct attributable costs	Patient/year	Mean	7855	NA	COPD	1998-2010	Denmark
Lou, P; et al. 2012	Direct costs	Patient/year	Mean	14326	NA	COPD	2008-2009	China

Table 2A. Continued

Study	Type of outcome	Outcome specified as	Assessment type	Study design	Point estimate	Reported NCDs	Year	Country
Mandelblatt, JS; et al. 2006	Direct costs	Patient/year	Mean	2491	4215	COPD	2000	USA
Mapel, DW; et al. 2000	Direct attributable costs	Patient/year	Mean	8512	NA	COPD	1997	USA
Mapel, DW; et al. 2000	Direct costs	Patient/year	Mean	16949	NA	COPD	1997	USA
Marton, JP; et al. 2006	Direct costs	Patient/year	Mean	17042	NA	COPD	2001	USA
Meen, P; et al. 2012	Direct costs	Patient/year	Mean	3826	NA	COPD	2006-2009	Germany
Meen, P; et al. 2012	Direct costs	Patient/year	Mean	3826	NA	COPD	2006-2009	Germany
Menzin, J; et al. 2008	Direct costs	Patient/year	Mean	34101	60664	COPD	2004	USA
Miravitlles, M; et al. 2003	Direct costs	Patient/year	Mean	2374	4908	COPD	2003	Spain
Nielsen, R; et al. 2009	Direct costs	Patient/year	Mean	431	NA	COPD	2003-2004	Norway
Nielsen, R; et al. 2009	Direct costs	Patient/year	Mean	725	NA	COPD	2003-2004	Iceland
Nielsen, R; et al. 2011	Direct costs	Patient/year	Mean	13583	NA	COPD	2005-2006	Norway
Nishimura, S; Zaher, C; 2004	Direct costs	Patient/year	Mean	1311	NA	COPD	1990-2002	Japan
Ray, GT; et al. 2000	Direct attributable costs	Patient/year	Mean	10176	NA	COPD	1995-1996	USA
Ray, GT; et al. 2000	Direct costs	Patient/year	Mean	25644	NA	COPD	1995-1996	USA
Rutten-Van Molken, MPMH; et al. 1999	Direct costs	Patient/year	Mean	1413	NA	COPD	1993	Netherlands
Schneider, KM; et al. 2009	Direct attributable costs	Patient/year	Mean	22183	NA	COPD	2001-2005	USA
Schneider, KM; et al. 2009	Direct costs	Patient/year	Mean	25547	NA	COPD	2001-2005	USA
Sharafkhaneh, A; et al. 2010	Direct costs	Patient/year	Mean	6083	NA	COPD	1997-2004	USA

Table 2A. Continued

Study	Type of outcome	Outcome specified as	Assessment type	Study design	Point estimate	Reported NCDs	Year	Country
Simoni-Wastila, L; et al. 2009	Direct costs	Patient/year	Mean	8819	16099	COPD	2003-2005	USA
Van Boven, JFM; et al. 2013	Direct costs	Patient/year	Mean	1419	NA	COPD	2009	Netherlands
Yoon, J; et al. 2011	Direct costs	Patient/year	Mean	6616	NA	COPD	2000	USA
Yoon, J; et al. 2011	Direct costs	Patient/year	Mean	6112	NA	COPD	2008	USA
Schneider, KM; et al. 2009	Direct attrbitutable costs	Patient/year	Mean	22183	NA	COPD	2005	USA
Schneider, KM; et al. 2009	Direct costs	Patient/year	Mean	25548	NA	COPD	2005	USA
Baumeister, SE; et al. 2009	Direct costs	Patient/year	Mean	5439	13350	CKD	2004-2005	Germany
Laliberte, F; et al. 2009	Direct costs	Patient/year	Mean	18314	52839	CKD	2000-2006	USA
Lamping, DL; et al. 2000	Direct costs	Patient/year	Mean	71824	NA	CKD	1995-1996	UK
Lee, H; et al. 2002	Direct costs	Patient/year	Mean	58871	27814	CKD	1999-2000	Canada
Schneider, KM; et al. 2009	Direct attributable costs	Patient/year	Mean	28462	NA	CKD	2001-2005	USA
Schneider, KM; et al. 2009	Direct costs	Patient/year	Mean	31826	NA	CKD	2001-2005	USA
Yoon, J; et al. 2011	Direct costs	Patient/year	Mean	23785	NA	CKD	2000	USA
Ray, GT; et al. 2000	Direct attributable costs	Patient/year	Mean	33585	NA	CKD	1996	USA
Ray, GT; et al. 2000	Direct costs	Patient/year	Mean	49286	NA	CKD	1996	USA
Yoon, J; et al. 2011	Direct costs	Patient/year	Mean	17681	NA	CKD	2008	USA
Schneider, KM; et al. 2009	Direct costs	Patient/year	Mean	31827	NA	CKD	2005	USA
Schneider, KM; et al. 2009	Direct attributable costs	Patient/year	Mean	28462	NA	CKD	2005	USA
Ballesta, M; et al. 2006	Direct costs	Patient/year	Mean	3714	NA	DM	1999	Spain

Table 2A. Continued

Study	Type of outcome	Outcome specified as	Assessment type	Study design	Point estimate	Reported NCDs	Year	Country
Biorac, N; et al. 2009	Direct costs	Patient/year	Mean	901	NA	DM	2007	Serbia
Chodick, G; et al. 2005	Direct costs	Patient/year	Mean	2653	NA	DM	1999	Israel
Chodick, G; et al. 2005	Direct costs	Patient/year	Mean	3010	NA	DM	2000	Israel
Chodick, G; et al. 2005	Direct costs	Patient/year	Mean	3422	NA	DM	2001	Israel
Costantino ME; et al. 2014	Direct costs	Patient/year	Mean	9731	NA	DM	2009	USA
Costantino ME; et al. 2014	Direct attributable costs	Patient/year	Mean	3390	NA	DM	2009	USA
Degli Esposti, L; et al. 2013	Direct costs	Patient/year	Mean	2291	5164	DM	2009	Italy
Elrayah-Eliadarous, H; et al. 2010	Direct costs	Patient/year	Mean	215	166	DM	2005	Sudan
Jonsson, B 2002	Direct costs	Patient/year	Mean	4092	NA	DM	1999	Europe
Kangas, T; et al. 1996	Direct costs	Patient/year	Mean	7408	NA	DM	1987-1989	Finland
Kirigia, JM; et al. 2009	Direct costs	Patient/year	Mean	1377	NA	DM	2000	Africa
Kumar, A; et al. 2008	Direct Cost	Patient/year	Mean	162	NA	DM	2005-2005	India
Le, C; et al. 2013	Direct costs	Patient/year	Mean	952	NA	DM	2010-2011	China
Martin, S; et al. 2007	Direct costs	Patient/year	Mean	2818	3276	DM	1995-2003	Germany
Morsanutto, A; et al. 2006	Direct costs	Patient/year	Mean	2452	NA	DM	2001-2002	Italy
Norlund, A; et al. 2001	Direct costs	Patient/year	Mean	7570	NA	DM	1992-1993	Sweden
Nakamura, K; 2008	Direct costs	Patient/year	Mean	4416	NA	DM	1990-2001	Japan
Oglesby, AK; et al. 2006	Direct attributable costs	Patient/year	Mean	2077	NA	DM	1989-2003	USA
Oliva, J; et al. 2004	Direct costs	Patient/year	Mean	1775	NA	DM	2002	Spain

Table 2A. Continued

Study	Type of outcome	Outcome specified as	Assessment type	Study design	Point estimate	Reported NCDs	Year	Country
Petersen, M; Amer Diabet, A 2008	Direct costs	Capita/year	Mean	13196	NA	DM	2007	USA
Petersen, M; Amer Diabet, A 2008	Direct attributable costs	Capita/year	Mean	7471	NA	DM	2007	USA
Ray, NF; et al. 1998	Direct costs	Capita/year	Mean	14617	NA	DM	1997	USA
Ray, NF; et al. 1998	Direct attributable costs	Capita/year	Mean	10743	NA	DM	1997	USA
Ringborg, A; et al. 2008	Direct costs	Patient/year	Mean	4047	9525	DM	2000-2004	Sweden
Tunceli, O; et al. 2010	Direct attributable costs	Patient/year	Mean	3373	13198	DM	2006-2009	USA
Tunceli, O; et al. 2010	Direct costs	Patient/year	Mean	4329	13198	DM	2006-2009	USA
Ray, GT; et al. 2000	Direct attributable costs	Patient/year	Mean	2444	NA	DM	1996	USA
Ray, GT; et al. 2000	Direct Costs	Patient/year	Mean	9462	NA	DM	1996	USA
Schneider, KM; et al. 2009	Direct attributable costs	Patient/year	Mean	12246	NA	DM	2005	USA
Schneider, KM; et al. 2009	Direct costs	Patient/year	Mean	15611	NA	DM	2005	USA

AMI=acute myocardial infarction, CAD=coronary artery disease, CHD=coronary heart disease, CKD=chronic kidney disease, COPD=chronic obstructive pulmonary disorder, CVD=cardiovascular disease, DM=diabetes mellitus, HF=heart failure, IHD=ischemic heart disease, NA=not applicable, NCDs=non-communicable disease, SD=standard deviation.

Table 2B. Results of the included studies investigating annual indirect costs of NCDs.

Study	Type of outcome	Outcome specified as	Assessment type	Point estimate	SD for mean	Reported NCDs	Year	Country
Sasser, AC; et al. 2005	Indirect costs	Patient/year	Mean	6752	NA	CVD	2000	USA
Hu, S; et al. 2013	Indirect costs	Patient/year	Mean	2644	NA	Stroke	2011	China
Lopez-Batista, J; et al. 2012	Indirect costs	Patient/year	Mean	23418	19558	Stroke	2004	Spain
Winter, Y; et al. 2008	Indirect costs	Patient/year	Mean	4018	4634	Stroke	2003	Germany
Jaworski, R; et al. 2012	Indirect costs	Patient/year	Mean	1780	NA	CAD	2005	Poland
Broekx, S; et al. 2011	Indirect costs	Patient/year	Mean	23692	NA	Breast cancer	2004	Belgium
Sasser, AC; et al. 2005	Indirect costs	Patient/year	Mean	11145	NA	Breast cancer	2000	USA
Sorensen, SV; et al. 2012	Indirect costs	Patient/year	Mean	24740	NA	Breast cancer	2007	USA
Wan, Y; et al. 2013	Indirect costs	Patient/year	Mean	2109	NA	Breast cancer	2009	USA
Darkow, T; et al. 2007	Indirect costs	Patient/year	Mean	3393	NA	COPD	2001-2004	USA
Fletcher, MJ; et al. 2011	Indirect costs	Patient/year	Mean	910	NA	COPD	2009	Cross-country
Jansson, SA; et al. 2002	Indirect costs	Patient/year	Mean	970	NA	COPD	1998-1999	UK
Lokke, A; et al. 2014	Indirect costs	Patient/year	Mean	3264	NA	COPD	1998-2010	Denmark
Nishimura, S; Zaher, C; 2004	Indirect costs	Patient/year	Mean	326	NA	COPD	1990-2002	Japan
Ballesta, M; et al. 2006	Indirect costs	Patient/year	Mean	2675	NA	DM	1999	Spain
Biorac, N; et al. 2009	Indirect costs	Patient/year	Mean	104	NA	DM	2007	Serbia

Table 2B. Contnuied

Study	Type of outcome	Outcome specified as	Assessment type	Point estimate	SD for mean	Reported NCDs	Year	Country
Le, C; et al. 2013	Indirect costs	Patient/year	Mean	7797	NA	DM	2010-2011	China
Kirigia, JM; et al. 2009	Indirect costs	Patient/year	Mean	2958	NA	DM	2000	Africa
Norlund, A; et al. 2001	Indirect costs	Patient/year	Mean	5350	NA	DM	1992-1993	Sweden

CAD=coronary artery disease, COPD=chronic obstructive pulmonary disorder, CVD=cardiovascular disease, DM=diabetes mellitus, NA=not applicable, NCDs=non-communicable disease, SD=standard deviation.

Table 2C. Results of the included studies investigating annual total costs of NCDs.

Study	Type of outcome	Outcome specified as	Assessment type	Point estimate	SD for mean	Reported NCDs	Year	Country
Sasser, AC; et al. 2005	Total costs	Patient/year	Mean	23065	NA	CVD	2000	USA
Hu, S; et al. 2013	Total costs	Patient/year	Mean	7422	NA	Stroke	2011	China
Lopez-Batista, J; et al. 2012	Total costs	Patient/year	Mean	44937	18535	Stroke	2004	Spain
Winter, Y; et al. 2008	Total costs	Patient/year	Mean	11396	NA	Stroke	2003	Germany
Jaworski, R; et al. 2012	Total costs	Patient/year	Mean	3423	NA	CHD	2005	Poland
2 Sorensen, SV; et al. 012	Total costs	Patient/year	Mean	105310	NA	Metastatic Breast cancer	2007	USA
Broekx, S; et al. 2011	Total attributable costs	Patient/year	Mean	26680	NA	Breast cancer	2004	Belgium
Sasser, AC; et al. 2005	Total costs	Patient/year	Mean	29988	NA	Breast cancer	2000	USA
Warren, JL; et al. 2008	Total costs	Patient/year	Mean	26492	NA	Breast cancer	1991-2002	USA
Kang, S; et al. 2012	Total costs	Patient/year	Mean	4964	NA	Lung cancer	2008	Australia
Warren, JL; et al. 2008	Total costs	Patient/year	Mean	50495	NA	Lung cancer	1991-2002	USA
Warren, JL; et al. 2008	Total costs	Patient/year	Mean	52068	NA	Colorectal cancer	1991-2002	USA
Jansson, SA; et al. 2002	Total costs	Patient/year	Mean	1662	NA	COPD	1998-1999	UK
Lokke, A; et al. 2014	Total Costs	Patient/year	Mean	15585	NA	COPD	1998-2010	Denmark
Nishimura, S; Zaher, C; 2004	Total costs	Patient/year	Mean	1637	NA	COPD	1990-2002	Japan

Table 2C. Continued

Study	Type of outcome	Outcome specified as	Assessment type	Point estimate	SD for mean	Reported NCDs	Year	Country
Ballesta, M; et al. 2006	Total costs	Patient/year	Mean	6206	NA	DM	1999	Spain
Biorac, N; et al. 2009	Total costs	Patient/year	Mean	1005	NA	DM	2007	Serbia
Le, C; et al. 2013	Total costs	Patient/year	Mean	8749	NA	DM	2010-2011	China
Kirigia, JM; et al. 2009	Total costs	Patient/year	Mean	4336	NA	DM	2000	Africa
Norlund, A; et al. 2001	Total costs	Patient/year	Mean	12920	NA	DM	1992-1993	Sweden

CHD=coronary heart disease, COPD=chronic obstructive pulmonary disorder, CVD=cardiovascular disease, DM=diabetes mellitus, NA=not applicable, NCDs=non-communicable disease, SD=standard deviation.

Table 3A. Healthcare expenditure and total direct costs associated with NCDs.

Study	Type of outcome	Outcome specified as	Assessment type	Point estimate	Reported NCDs	Year	Country
Hodgson, TA; Cohen, AJ 1999	Direct costs	Per year	Mean	195.4 million	CVD	1995	USA
Nichols, GA; et al. 2010	Direct costs	Per year	Mean	400 billion	CVD	2000-2008	USA
Leal, J; et al. 2006	Direct costs	Per year	EUR	151.3 billion	CVD	2003	Europe (cross-country)
Leigh, JP; et al. 2003[a]	Direct costs	Per year	Mean	15.53 billion	CVD, Cancer, COPD	1999	USA
Odden, MC; et al. 2011	Direct costs	Per year	Mean	130.6 billion	CVD, CHD	2010	USA
Hodgson, TA; Cohen, AJ 1999	Direct costs	Per year	Mean	59.1 million	CHD	1995	USA
Leal, J; et al. 2006	Direct costs	Per year	EUR	32.9 billion	CHD	2003	Europe (cross-country)
Caro, JJ; et al. 2006	Hospitalization costs	Per year	Mean	20.5 million	Stroke	1990-1995	France
Dewey, HM; et al. 2003	Hospitalization costs	Per year	Mean	164 million	Stroke	1997	Australia
Kolominsky-Rabas, PL; et al. 2006	Direct costs	Per year	Mean	10.6 billion	Stroke	2004	Germany
Simpson, A.N; et al. 2013[a]	Direct costs	Per year	Mean	133.41 million	CVD, Stroke	2004	USA
Beaulieu, N; et al. 2009	Medication costs	Per year	Mean	31.8 billion	Lung cancer	2009	Worldwide
Beaulieu, N; et al. 2009	Nonmedical costs	Per year	Mean	12.0 billion	Lung cancer	2009	Worldwide
Beaulieu, N; et al. 2009	Medication costs	Per year	Mean	20.2 billion	Colorectal cancer	2009	Worldwide
Beaulieu, N; et al. 2009	Nonmedical costs	Per year	Mean	7.9 billion	Colorectal cancer	2009	Worldwide
Selke, B; et al. 2003	Direct costs	Per year	Mean	564.59 million	Colorectal Cancer	1999	France

Table 3A. Continued

Study	Type of outcome	Outcome specified as	Assessment type	Point estimate	Reported NCDs	Year	Country
Boncz, I; et al. 2010	Direct costs	Per year	Mean	43.4 million	Colorectal cancer	2001	Hungary
Davari, M; et al. 2012	Direct costs	Per period of surveillance	Minimum	39.3 million	Colorectal cancer	2005-2010	Iran
Torres, US; et al. 2010	Direct costs	Per year	Mean	18.54 million	Colorectal cancer	1996	Brazil
Torres, US; et al. 2010	Direct costs	Per year	Mean	37.64 million	Colorectal cancer	2008	Brazil
Beaulieu, N; et al. 2009	Medication costs	Per year	Mean	14.2 billion	Breast cancer	2009	Worldwide
Beaulieu, N; et al. 2009	Nonmedical costs	Per year	Mean	8.3 billion	Breast cancer	2009	Worldwide
Boncz, I; et al. 2010	Direct costs	Per year	Mean	37.4 million	Breast cancer	2001	Hungary
Beaulieu, N; et al. 2009	Medication costs	Per year	Mean	865.4 million	Cervical cancer	2009	Worldwide
Beaulieu, N; et al. 2009	Nonmedical costs	Per year	Mean	703.6 million	Cervical cancer	2009	Worldwide
Boncz, I; et al. 2010	Direct costs	Per year	Mean	4.5 million	Cervical cancer	2001	Hungary
Aljunid, S; et al. 2010	Direct costs	Per year	Mean	12.98 million	Cervical cancer	2007-2008	Malysia
Gil, A; et al. 2007	Hospitalization costs	Per year	Mean	18.19 million	Cervical cancer	1999-2002	Spain
Low, JJ; et al. 2012	Direct cost	Per year	Mean	45.7 million	Cervical cancer	2008-2033	Singapore

Table 3A. Continued

Study	Type of outcome	Outcome specified as	Assessment type	Point estimate	Reported NCDs	Year	Country
Yabroff, KR; et al. 2008	Aggregated costs	Per 5 years	Mean	26 billion	Lung, colorectal, cervical & breast cancer	1999-2003	USA
Yabroff, KR; et al. 2008	Aggregated costs	Per year	Mean	5,2 billion	Lung, colorectal, cervical & breast cancer	1999-2003	USA
Nielsen, R; et al. 2009	Direct costs	Per year	Mean	232.3 million	COPD	2003-2004	Iceland
Schneider, KM; et al. 2009	Direct costs	Per year	Mean	9.2 billion	COPD, CKD	2001-2005	USA
Chittleborough, CR; et al. 2009	Direct costs	Per year	Mean	162 million	COPD, DM	2001-2002	Australia
Chodick, G; et al. 2005	Direct costs	Per year	Mean	1159.2 million	DM	2001	Israel
Dewey, HM; et al. 2001	Direct costs	Per year	Mean	82.12 million	CVD, Stroke	1997	Australia
Hogan, P; et al. 2003	Direct attributable costs	Per year	Mean	119 billion	DM	2002	USA
Hogan, P; et al. 2003	Direct costs	Per year	Mean	160 billion	DM	2002	USA
Jonsson, B 2002	Direct costs	Per year	Mean	41.1 billion	DM	1999	Europe
Kirigia, JM; et al. 2009	Direct costs	Per year	Mean	9.7 billion	DM	2000	Africa
Oliva, J; et al. 2004	Direct costs	Per year	Mean	3.25 billion	DM	2002	Spain
Oliva, J; et al. 2004	Hospitalization costs	Per year	Mean	1096 million	DM	1999	Spain

Table 3A. Continued

Study	Type of outcome	Outcome specified as	Assessment type	Point estimate	Reported NCDs	Year	Country
Oliva, J; et al. 2004	Hospitalization costs	Per year	Mean	1198 million	DM	2002	Spain
Petersen, M; Amer Diabet, A 2008	Direct costs	Per year	Mean	230.5 million	DM	2007	USA
Petersen, M; Amer Diabet, A 2008	Direct attributable costs	Per year	Mean	130.3 billion	DM	2007	USA
Ray, NF; et al. 1998	Direct costs	Per year	Mean	112.8 billion	DM	1989-1995	USA
Ray, NF; et al. 1998	Direct attributable costs	Per year	Mean	64 billion	DM	1997	USA

[a] Studies limited in a certain number of population, not for the entire country.
CHD=coronary heart disease, CKD=chronic kidney disease, COPD=chronic obstructive pulmonary disorder, CVD=cardiovascular disease, DM=diabetes mellitus, NA=not applicable, NCDs=non-communicable disease.

Table 3B. Annual income losses (indirect costs) associated with NCDs.

Study	Type of outcome	Outcome specified as	Assessment type	Point estimate	Reported NCDs	Year	Country
Hogan, P; et al. 2003	Indirect attributable costs	Per year	Mean	52 billion	DM	2002	USA
Kirigia, JM; et al. 2009	Indirect costs	Per year	Mean	20.8 billion	DM	2000	Africa
Leal, J; et al. 2006	Indirect costs	Per year	Mean	92921 million	CVD	2003	Europe (cross-country)
Dewey, HM; et al. 2001	Indirect costs	Per year	Mean	51.71 million	CVD, Stroke	1997	Australia
Leal, J; et al. 2006	Indirect costs	Per year	Mean	31835 million	CHD	2003	Europe (cross-country)
Selke, B; et al. 2003	Indirect costs	Per year	Mean	679.12 million	Colorectal Cancer	1999	France
Petersen, M; Amer Diabet, A 2008	Indirect attributable costs	Per year	Mean	65.2 billion	DM	2007	USA
Ray, NF; et al. 1998	Indirect attributable costs	Per year	Mean	78.3 billion	DM	1997	USA
Klever-Deichert, G; et al. 1999	Indirect costs	Per year	Mean	71 billion	CVD	1996	Germany
Nichols, GA; et al. 2010	Indirect costs	Per year	Mean	600 billion	CVD	2000-2008	USA
Zheng, H; et al. 2010	Indirect costs	Per year	Mean	2.21 billion	CHD	2004	Australia
Beaulieu, N; et al. 2009	Productivity loss	Per year	Mean	13.7 billion	Lung cancer	2009	Worldwide
Beaulieu, N; et al. 2009	Productivity loss	Per year	Mean	8.2 billion	Colorectal cancer	2009	Worldwide
Beaulieu, N; et al. 2009	Productivity loss	Per year	Mean	1.7 billion	Cervical cancer	2009	Worldwide
Beaulieu, N; et al. 2009	Productivity loss	Per year	Mean	8.4 billion	Breast cancer	2009	Worldwide

Table 3B. Continued

Study	Type of outcome	Outcome specified as	Assessment type	Point estimate	Reported NCDs	Year	Country
Aljunid, S; et al. 2010	Indirect costs	Per year	Mean	4.11 million	Cervical cancer	2007-2008	Malaysia
Van Boven, JFM; et al. 2013	Indirect costs	Per year	Mean	388.6 million	COPD	2009	Netherlands

CHD=coronary heart disease, COPD=chronic obstructive pulmonary disorder, CVD=cardiovascular disease, DM=diabetes mellitus, NCDs=non-communicable disease.

Table 3C. Healthcare expenditure and national income losses (direct and indirect costs) associated with NCDs.

Study	Type of outcome	Outcome specified as	Assessment type	Point estimate	Reported NCDs	Year	Country
Klever-Deichert, G; et al. 1999	Direct + indirect costs	Lifetime	Mean	108.9 billion	CVD	1999	Germany
Nichols, GA; et al.							
Nichols, GA; et al. 2010	Direct + indirect costs	Per year	Mean	1 trillion	CVD	2000-2008	USA
Dewey, HM; et al. 2003	Direct + indirect costs	Lifetime	Mean	1.3 billion	Stroke	1997	Australia
Dewey, HM; et al. 2001	Direct + indirect costs	Per year	Mean	868.8 million	CVD, Stroke	1997	Australia
Mittman, N; et al. 2012	Direct + indirect costs	Per year	Mean	3.47 billion	CVD, Stroke	2005-2009	Canada
Taylor, TN; et al. 1996	Direct + indirect costs	Lifetime	Mean	72.37 billion	CVD, Stroke	1990-1993	USA
Leal, J; et al. 2006	Direct + indirect costs	Per year	Mean	244249 million	CVD	2003	Europe (cross-country)
Leal, J; et al. 2006	Direct + indirect costs	Per year	Mean	64.7 billion	CHD	2003	Europe (cross-country)
Beaulieu, N; et al. 2009	Direct + indirect costs	Per year	Mean	57.4 billion	Lung cancer	2009	Worldwide
Warren, JL; et al. 2008	Direct + indirect costs	Per year	Mean	2.5 billion	Lung cancer	1991-2002	USA
Beaulieu, N; et al. 2009	Direct + indirect costs	Per year	Mean	36.3 billion	Colorectal cancer	2009	Worldwide
Selke, B; et al. 2003	Direct + indirect costs	Per year	Mean	1.24 billion	Colorectal Cancer	1999	France
Warren, JL; et al. 2008	Direct + indirect costs	Per year	Mean	2.5 billion	Colorectal cancer	1991-2002	USA

Table 3C. Continued

Study	Type of outcome	Outcome specified as	Assessment type	Point estimate	Reported NCDs	Year	Country
Beaulieu, N; et al. 2009	Direct + indirect costs	Per year	Mean	3.2 billion	Cervical cancer	2009	Worldwide
Aljunid, S; et al. 2010	Direct + indirect costs	Per year	Mean	17.08 million	Cervical cancer	2007-2008	Malaysia
Beaulieu, N; et al. 2009	Direct + indirect costs	Per year	Mean	30.9 billion	Breast cancer	2009	Worldwide
Jansson, SA; et al. 2002	Direct + indirect costs	Per year	Mean	1.1 billion	COPD	1998-1999	Sweden
Nishimura, S; Zaher, C; 2004	Direct + indirect costs	Per year	Mean	9.1 billion	COPD	1990-2002	Japan
Van Boven, JFM; et al. 2013	Direct + indirect costs	Per year	Mean	133.7 million	COPD	2009	Netherlands
Hogan, P; et al. 2003	Total attributable costs (Direct + indirect)	Per year	Mean	171 billion	DM	2002	USA
Kirigia, JM; et al. 2009	Direct + indirect costs	Per year	Mean	30.4 billion	DM	2000	Africa
Le, C; et al. 2013	Direct + indirect costs	Per year	Mean	46.7 million	DM	2010-2011	China
Petersen, M; Amer Diabet, A 2008	Direct + indirect costs	Per year	Mean	195.5 billion	DM	2007	USA
Ray, NF; et al. 1998	Direct + indirect costs	Per year	Mean	142.5 billion	DM	1997	USA

CHD=coronary heart disease, COPD=chronic obstructive pulmonary disorder, CVD=cardiovascular disease, DM=diabetes mellitus, NCDs=non-communicable disease.

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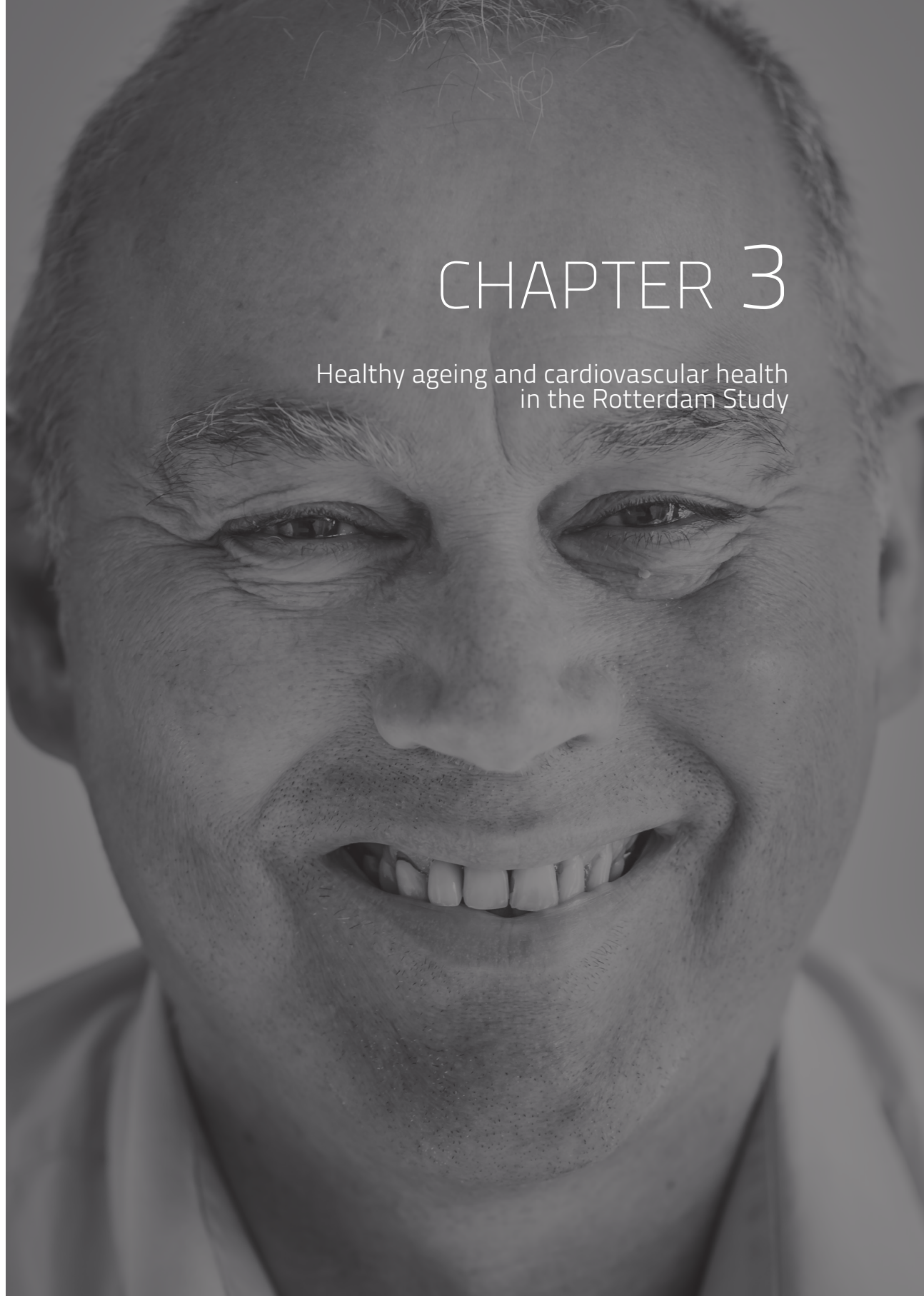
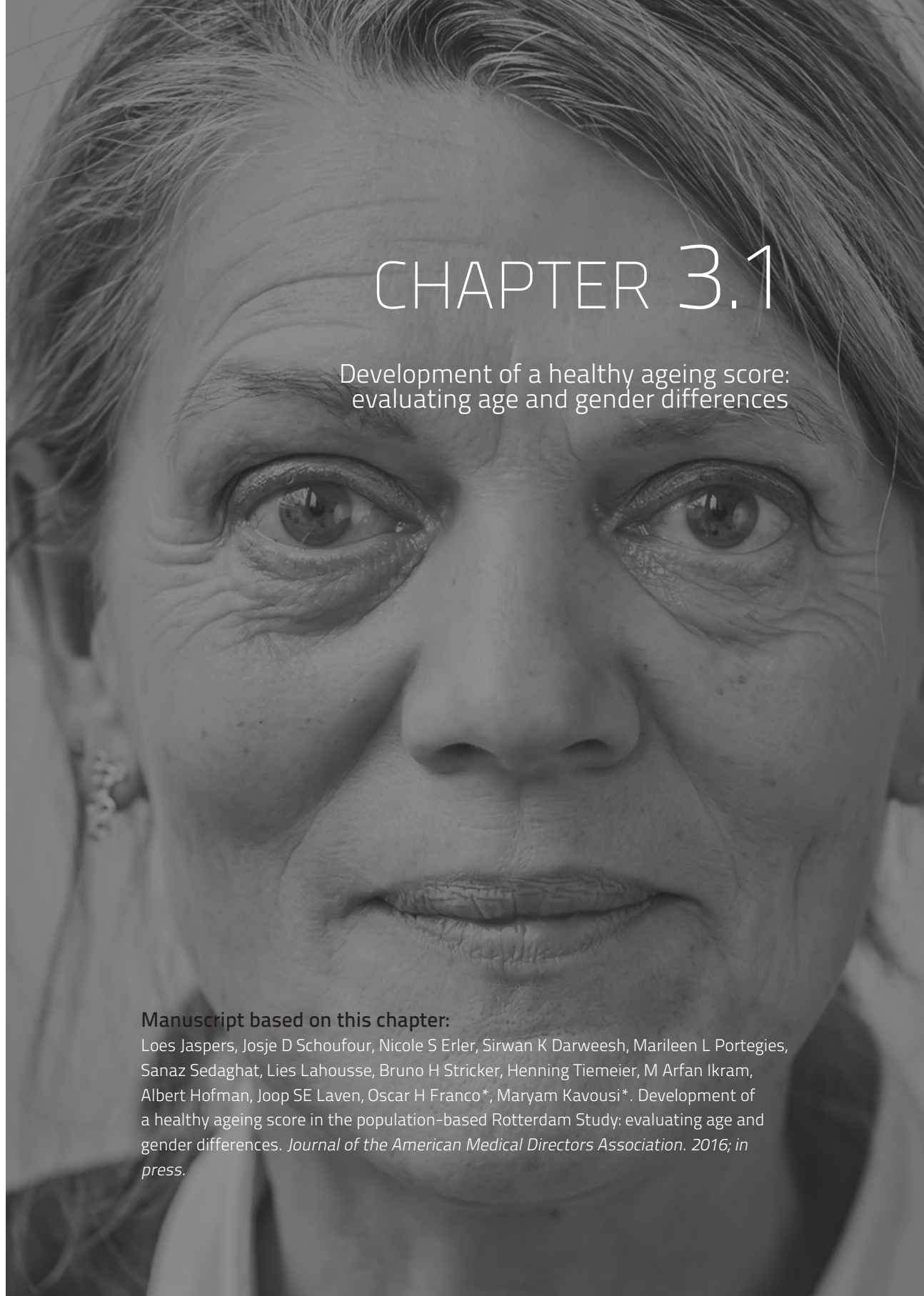


CHAPTER 3

Healthy ageing and cardiovascular health in the Rotterdam Study



CHAPTER 3.1

Development of a healthy ageing score: evaluating age and gender differences

Manuscript based on this chapter:

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ABSTRACT

Background:
Given the increasing life expectancy and transition from infectious to chronic diseases, healthy ageing is a key public health challenge of growing importance.

Objectives:
To develop a healthy ageing score (HAS), to assess age and gender differences in HAS, and to evaluate the association of the HAS with survival.

Design:
Prospective population-based cohort.

Setting:
Inhabitants of Ommoord, Rotterdam, the Netherlands.

Participants:
1405 men and 2122 women, mean (standard deviation, SD) age 75.9 (6.4) years.

Main measures:
We included 7 domains in the total score of HAS: chronic diseases, mental health, cognitive function, physical function, pain, social support, and quality of life; each scored 0, 1, or 2 in each domain. A total score (range 0-14) was constructed and was assessed continuously and in tertiles (13-14: healthy ageing, 11-12: intermediate ageing, 0-10: poor ageing). Gender-specific change in the mean HAS was computed for the age categories of 65-69, 70-74, 75-79, 80-84, and ≥85 years. The association between HAS and mortality was assessed with Cox Proportional Hazards models.

Results:
Mean follow-up was 8.6 (3.4) years. Men had poorer scores in the chronic disease domain than women. However, women had poorer mental health, worse physical function, more pain, and lower quality of life compared to men. The prevalence of healthy ageing was higher in men (n=396, 28.2%), than in women (n=526, 24.8%). The mean (SD) HAS was 11.1 (2.2) in men and 10.7 (2.3) in women. Mean HAS was higher in men than in women for all age categories. The ß for change in mean HAS across the 5 increasing age categories was -0.55 (-0.65 to -0.45) in men and -0.65 (-0.73 to -0.57) in women. The age-adjusted hazard ratio per unit increase in HAS with mortality was 0.86 (0.83 to 0.89) in men, and 0.89 (0.87 to 0.91) in women.

Conclusions:
Levels of HAS were lower in women compared to men, in all age categories. The HAS declined with increasing age for both genders, albeit slightly steeper in women. The HAS was strongly associated with mortality in both genders. A better understanding of population healthy ageing and gender differences in this regard could aid to implement strategies for sustainable healthcare in ageing populations.

Keywords:
healthy ageing, age differences, gender differences, mortality, longevity, epidemiology

INTRODUCTION

Our population is ageing.[1 2] Between 2008 and 2040, the proportion of people aged 65 years and older is projected to increase from 7% (506 million) to 14% (1.3 billion) of the world's population.[3] Additionally, the number of oldest old (aged 80 and over), is expected to increase by 233% in this time period.[3] This demographic shift can be explained by better living standards and improvements in both preventive and curative health care.[4] Simultaneously, the main causes of death have shifted from infectious diseases towards age-related chronic diseases.[5] These observed trends have led to ageing, and particularly healthy ageing, to become one of the top public health challenges,[6 7] and resulted in the first World Report on Ageing and Health from the World Health Organization in 2015.[8]

Focusing on health as a multidimensional state could facilitate prevention and treatment strategies.[9] Theoretical frameworks have been formulated,[10-14] and various operational definitions have been applied to populations.[15 16] For example, Rowe and Kahn introduced a model for successful ageing, that included avoiding disease and disability, high cognitive and physical function, and engagement with life.[13 14] This model has been critiqued for being too unidimensional, with its strong focus on physiological constructs for successful ageing.[17] Therefore, recent applications have comprehensively included psychosocial constructs, such as mental health, and self-perceived health.[18-20] Additionally, it has been suggested that continuum-based measures for healthy ageing might better capture the heterogeneity of the phenotype, as opposed to the more widely adopted dichotomous approaches.[19 21] However, to date, no consensus for the measurement of healthy ageing exists.

Worldwide, women outlive men by 6 to 8 years. However, these years are often spent with more disease and disability: 'men die quicker, women get sicker'.[9 22] Whereas the operationalization of healthy ageing measures is upcoming, no studies have comprehensively assessed age and gender differences. Within the population-based Rotterdam Study, comprehensive and detailed information on subjective and objective measures, which are necessary to construct a healthy ageing score, are available. In addition, the vital status of all participants has been precisely adjudicated in this cohort of middle-aged and elderly men and women. Therefore, we aimed to develop a healthy ageing score (HAS) within the population-based Rotterdam Study and to assess age and gender differences. Furthermore, for illustrative purposes, we aimed to evaluate the association of the HAS with survival.

METHODS

Study population

This study was embedded within the Rotterdam Study: a prospective, population-based cohort among subjects 55 years and older in the municipality of Rotterdam, the Netherlands. The rationale and study design have been described elsewhere.[23] The baseline examination of the original cohort was completed between 1990 and 1993 (RS-I, visit 1). In the fourth visit of RS-I (2002-2004), assessments of social support and quality of life were introduced. Therefore, the current study included all participants alive at the fourth visit of RS-I. Of the 5.008 participants available for inclusion, 1.481 were excluded due to missing data in more than 5 domains of the HAS. Hence, 1405 men and 2122 women were included in the current study. The Rotterdam Study has been approved by the Medical Ethics Review Board of Erasmus Medical Center and by the Ministry of Health, Welfare and Sport of the Netherlands, implementing the Wet Bevolkingsonderzoek: ERGO (Population Studies Act: Rotterdam Study). All participants provided written informed consent to participate in the study and to obtain information from their treating physicians.

Assessment of healthy ageing score

In line with previously defined conceptual frameworks and applications,[10-21] we included 7 biopsychosocial domains in the development and construction of the healthy ageing score. These domains involved: chronic diseases, mental health, cognitive function, physical function, pain, social support, and quality of life. In each domain, the status was graded as low (0, corresponding to a worse status within the domain), moderate (1), or high (2, corresponding to an optimal status within the domain); *Scheme 1*. A total score, ranging from 0 to 14 was constructed, by summing up the values of these 7 domains. An extensive description of the HAS construction can be found in *Supplemental Methods 1A*.

Assessment of all-cause mortality

In order to ascertain death and cause of death for all participants of the Rotterdam Study, mortality data was obtained via complementary approaches.[23] Data sources included the central registry of the Municipality of Rotterdam, records from collaborating general practitioners, and information from follow-up rounds. The Central Registry of Genealogy of the Netherlands was consulted when the vital status of participants were missing. All-cause mortality was available up to October 1st, 2015.

Assessment of covariates

The following socio-economic and health behaviour factors were considered for inclusion as covariates in multivariable adjusted models examining the association of HAS with mortality: baseline age, education, household income, marital status, ethnicity, smoking, physical activity, dietary habits, alcohol intake, and waist-hip ratio. A description of the data collection procedure and coding of each covariate is provided in *Supplemental Methods 1B*.

Statistical analyses

Participant characteristics were described using means (standard deviations (SD)) and

Scheme 1. Definition of healthy ageing score.

Domain	Low (score of 0)	Moderate (score of 1)	High (score of 2)
Chronic diseases[a]	> 1 disease, 'multimorbidity'	1 disease	0 diseases
Mental health CES-D	Score of 23-60	Score of 17-22	Score of 0-16 (no depressive symptoms)
Cognitive functioning MMSE	Score of 0-20	Score of 21-25	Score of 26-30
Physical functioning bADL/iADL	Severe disability on either bADL or iADL	Everything in between	Mild disability on bADL and iADL
Pain	(Very) severe pain in hands, knees, hips or back for at least 1 activity	Everything in between	No or mild pain in hands, knees, hips and back in all activities
Social support	'Agree' in 0-2 statements	'Agree' in 3-4 statements	'Agree' for all 5 statements
Quality of life	Low QoL on 5-8 items	Low QoL on 1-4 items	High QoL on all 8 items

[a] Chronic diseases included: myocardial infarction, revascularization, heart failure, stroke, Parkinson's disease, diabetes mellitus, chronic obstructive pulmonary disease, cancer, chronic kidney disease.
bADL=basic activities of daily living, CES-D= Center for Epidemiologic Studies Depression Scale, iADL=instrumental activities of daily living, MET=metabolic equivalent, MMSE=mini mental state examination, QoL=quality of life.

proportions. All analyses were stratified for gender, given that gender-based differences in health conditions, functioning, behaviour, and social relations may differentially affect patterns of healthy ageing.[8]

Characteristics of healthy ageing score

The correlation between the domains was assessed with Pearson correlation coefficients, and was considered high if it was ≥ 0.70.[24] Thereafter, the prevalence of low, moderate, and high categories for each of the 7 included domains was assessed. Differences between men and women were tested using the Chi^2 statistic.

The healthy ageing score was constructed from the 7 domains as a score ranging from 0 to 14. The HAS was assessed continuously as well as in tertiles. The distribution of HAS on a continuous scale was plotted using histograms. We calculated the mean HAS for men and women and additionally adjusted the mean HAS for age using linear regression analysis. We further evaluated and plotted the change of the mean HAS, stratified for age categories (65-69, 70-74, 75-79, 80-84, and ≥85 years) and gender. To define HAS tertiles, the cut-offs 12 and 10 were used for both men and women. Based on the tertiles, participants were categorized into 3 categories; healthy ageing (a score of 13-14), intermediate ageing (a score of 11-12), and poor ageing (a score of 0-10). Differences between men and women were tested using the Chi^2 statistic.

Survival analyses

In secondary analyses, the association between HAS with mortality was assessed. However, this was only done for illustrative purposes, given that the HAS was developed to assess health status' that extend beyond life or death.

The proportional hazards assumption was tested by evaluating log minus log survival plots. We developed two Cox Proportional Hazards models; an age-adjusted model (model 1) and a model further adjusted for covariates (model 2). To build model 2, we first selected the covariates that were associated with both the exposure (HAS) and the outcome (mortality) with a p-value below 0.2.[25] Thereafter, using the likelihood ratio test, covariates were eliminated from the multivariable model via a backward selection approach if their contribution to the model was not significant. Hence, model 2 included the covariates: age, smoking (current vs never), smoking (former vs never), dietary habits, physical activity, and waist-hip ratio. This model could be considered a conservative model given that these covariates antecedently affect the domains of HAS or could be an intermediate factor in the association between HAS with mortality. We also developed survival plots for tertiles of HAS for men and women. Considering the borderline significant interaction term for HAS*gender (p=0.082) and significant interaction term for HAS*age (p=0.006), we calculated age and gender-specific hazard ratio's (HRs) for HAS with mortality. HRs between the youngest and oldest age categories were compared using a test of interaction.[26]

Supplementary analyses

In order to reduce bias due to selective dropout of less healthy participants, values of the 7 domains and covariates were imputed for everybody alive at the start of the fourth visit of the Rotterdam Study and had values observed in at least 2 domains. None of the imputed variables had more than 35% missing data. Values were imputed using fully conditional specification (Markov chain Monte Carlo method) with a maximum iteration number of 20.

In sensitivity analyses, we compared the descriptive characteristics for the observed data to the data after multiple imputation. Moreover, we performed a comparison between the included participants in the study and the ones excluded. To evaluate the influence of choosing tertiles for categorical analyses of HAS, a second approach using the Youden Index was used. The Youden Index maximizes the sum of specificity and sensitivity, to attain an optimal cut-off value of healthy vs non-healthy ageing for mortality. In this scenario, having a score of 12 to 14 was categorized as healthy ageing whilst the remainder of the score was divided into 2 equal groups (a score of 10-11 for intermediate ageing and a score of 0-9 for poor ageing). Further sensitivity analyses included ruling out the possibility of reversed causality by excluding participants who died within the first 3 years after baseline and a complete case analysis.

Table 1. Characteristics of the study population.

General characteristics	Men (n=1405)	Women (n=2122)
Age, years	75.3 (6.0)	76.3 (6.6)
Education, n(%)		
Primary education	156 (11.1)	417 (19.7)
Lower/intermediate general or lower vocational education	440 (31.3)	1070 (50.4)
Intermediate vocational or higher general education	538 (38.3)	532 (25.1)
Higher vocational education or university	271 (19.3)	103 (4.8)
Household income, in /1000,-	2.6 (1.1)	2.2 (1.0)
Marital status, n(%)		
Never married	36 (2.6)	181 (8.5)
Married, living together	1124 (80.0)	919 (43.3)
Widowed, divorced	245 (17.4)	1022 (48.2)
Ethnicity, Caucasian	1372 (97.7)	2088 (98.4)
BMI, kg/m2	27.0 (3.5)	27.8 (4.6)
Waist-hip ratio	0.98 (0.07)	0.86 (0.07)
Smoking, n(%)		
Current	241 (17.1)	281 (13.2)
Former	1040 (74.0)	866 (40.8)
Never	124 (8.9)	975 (46.0)
Physical activity, MET-hours/week	78.6 (43.6)	94.4 (46.0)
Dutch Healthy Diet Index, score 0-100	42.3 (9.7)	47.8 (9.8)
Alcohol intake, gram/day	15.9 (16.7)	6.9 (9.7)

Values are numbers (percentages) or mean (SD) unless stated otherwise. Decimal values for numbers, originating from the combination of multiple imputation sets, were rounded to integer values.
BMI=body mass index, CKD=chronic kidney disease, COPD=chronic obstructive pulmonary disease, MET=metabolic equivalents, MI=myocardial infarction, n=number, SD=standard deviation.

All analyses were performed using IBM SPSS Statistics Version 21.0 and R statistical software (http://www.r-project.org), Version 3.3.1. Associations with a p-value below 0.05 were considered statistically significant.

RESULTS

Among the total population of 3527 participants, 1405 (39.8%) subjects were men and 2122 (60.2%) were women (*Table 1*). Mean (SD) age was 75.3 (6.0) years and 76.3 (6.6) years in men and women, respectively. Nearly all participants (>97%) were of Caucasian descent. Two hundred seventy-one men (19.3%) completed higher vocational education or university, whereas in women this number was 103 (4.8%). Furthermore, 1124 men were married or living with a partner (80.0%), compared to 919 women (43.3%).

Characteristics of healthy ageing score

The correlation between the separate domains ranged from 0 (correlation between chronic disease and social support) to 0.55 (correlation between mental health and quality of life) *(Supplemental Table 1*). *Table 2* provides the prevalence of the 3 categories (low, moderate, and high) for the 7 domains included in the healthy ageing score. Compared to men, more women were in the high category for absence of chronic disease (41.2% in

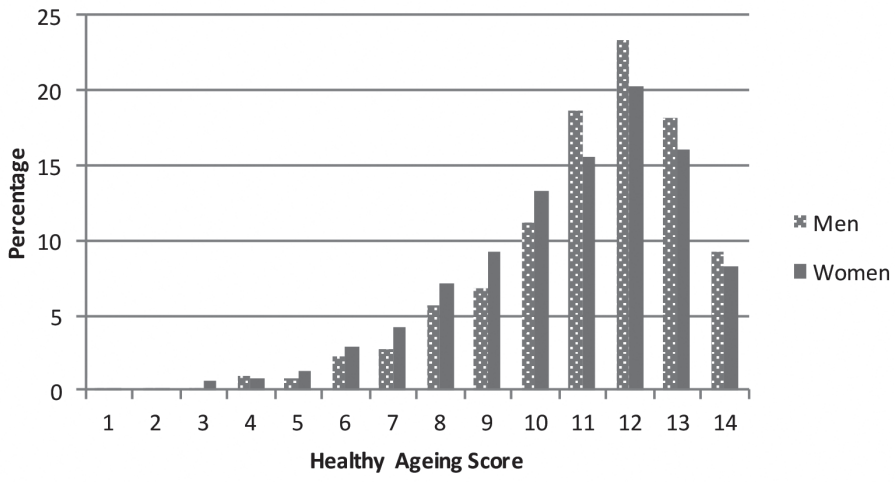
Table 2. Prevalence of low, moderate, and high categories for the 7 domains included in the healthy ageing score.

	Men (n=1405)			Women (n=2122)		
	Low (0)	Moderate (1)	High (2)	Low (0)	Moderate (1)	High (2)
Chronic disease	452 (32.2)	508 (36.2)	445 (31.6)	427 (20.1)**	820 (38.7)	875 (41.2)**
Mental health	54 (3.9)	70 (5.0)	1281 (91.1)	172 (8.1)**	204 (9.7)**	1746 (82.2)**
Cognitive function	35 (2.5)	182 (13.0)	1188 (84.5)	81 (3.8)*	292 (13.8)	1749 (82.4)
Physical function	54 (3.8)	234 (16.7)	1117 (79.5)	116 (5.5)*	459 (21.6)**	1547 (72.9)**
Pain	90 (6.4)	457 (32.5)	858 (61.1)	312 (14.7)**	870 (41.0)**	940 (44.3)**
Social wellbeing	124 (8.8)	369 (26.3)	912 (64.9)	184 (8.6)	508 (24.0)	1430 (67.4)
Quality of life	78 (5.6)	467 (33.2)	860 (61.2)	176 (8.3)*	837 (39.5)**	1109 (52.2)**

Values are numbers (percentages). Decimal values, originating from the combination of multiple imputation sets, were rounded to integer values.
* Difference between men and women, per category of the particular domain, statistically significant at α <0.05
** Difference between men and women, per category of the particular domain, statistically significant at α <0.001

women vs 31.6% in men). However, fewer women were in the high category for adequate mental health (82.2% in women vs 91.1% in men), good physical function (72.9% in women vs 79.5% in men), absence of pain (44.3% in women vs 61.1% in men), and good quality of life (52.2% in women vs 61.2% in men). These differences did not change after adjusting for age. The mean HAS was 11.1 (2.2) and 10.7 (2.3) in men and women, respectively, and remained the same after adjusting for age. The distribution of HAS for men and women was similar (*Figure 1*). However, the proportion of favourable healthy ageing scores was higher in men than in women. When looking at HAS in tertiles, the proportion of healthy agers was higher in men than in women (*Supplemental Table 2*). Furthermore, the mean

Figure 1. Distribution of the healthy ageing score for men and women.

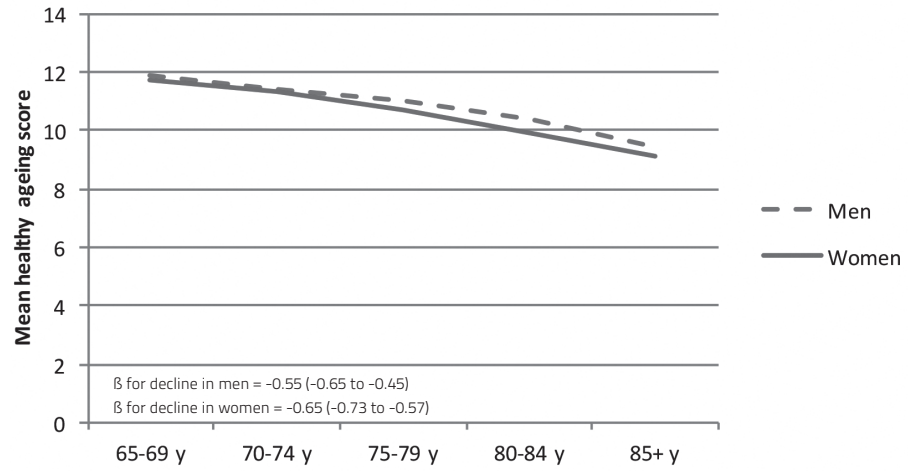


HAS decreased linearly across age categories, with borderline significant evidence for parabolic decline in both men (p=0.088) and women (p=0.059) (*Figure 2*). The ß for change in mean HAS across the 5 age categories was steeper in women (-0.65 (-0.73 to -0.57)) compared to men (-0.55 (-0.65 to -0.45)), but did not differ significantly by gender (p=0.12). Within age categories, the mean HAS was significantly higher in men aged 75-79 years (p=0.041) and aged 80-84 years (p=0.008) compared to women in the same age category.

Survival analyses

Overall, 793 men died during mean 8.1 years (SD 3.6) years of follow-up, and 1002 women died during mean 8.9 (SD 3.3) years of follow-up. Whereas cumulative survival in men decreased from the start of follow-up and the decline was gradual over time, in women cumulative survival remained high and dropped more steeply towards the end of follow-

Figure 2. Gender-specific change of the healthy ageing score across age groups.



up in age-adjusted model 1 (*Figures 3A and 3B*). This was the same for survival plots adjusted for covariates in conservative model 2 (*Supplemental Figures 1A and 1B*). For model 1 and model 2, the HRs per unit increase in HAS with mortality were 0.86 (0.83 to 0.89) and 0.87 (0.83 to 0.90) respectively in men, and 0.89 (0.87 to 0.91) and 0.90 (0.87 to 0.92) in women. Analyses were repeated for age and gender-strata (*Supplemental Table 3*). In women, the HR of the youngest age category was stronger than the HR of the oldest age category (p=0.02), whereas no differences were observed in men (p=0.77). To further explore this differential effect on mortality, the proportions of low, moderate, and high scores within each of the 7 HAS domains were stratified for gender and age groups (*Supplemental Table 4*). For the domains mental health and pain, fewer women were in the high category compared to men and this remained significantly different for all age categories.

Supplementary analyses

The observed data and the data after multiple imputation did not substantially differ (*Supplemental Table 5 and 6*). Moreover, we compared participants included in the study to those excluded. The included participants were younger, slightly higher educated and had a lower proportion of prevalent chronic disease, compared to the excluded participants (*Supplemental Table 7*).

Using the Youden Index, the optimal cut-off for healthy vs non-healthy ageing was 12. Analyses were repeated using this optimal cut-off for defining the healthy ageing categories. The proportion of healthy agers was now 50.9% in men and 44.1% in women.

Figure 3A. Age-adjusted survival plots for healthy ageing score in tertiles, for men.

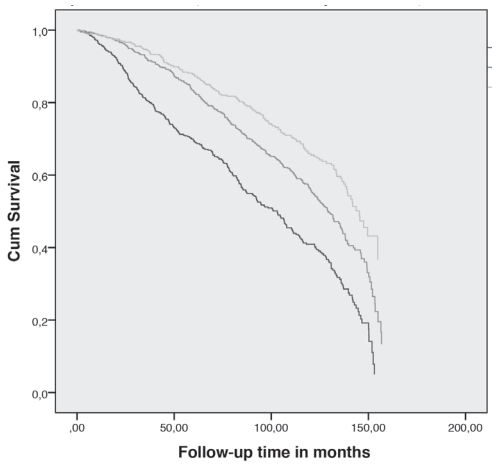
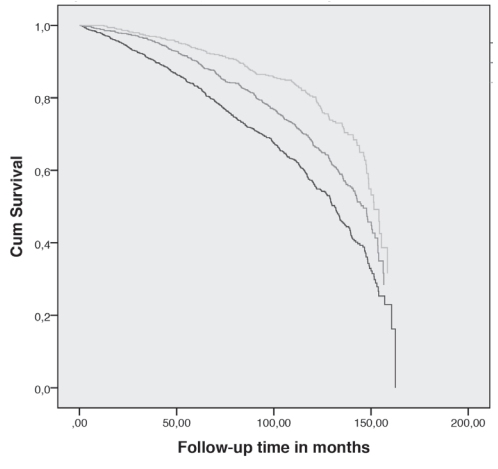


Figure 3B. Age-adjusted survival plots for healthy ageing score in tertiles, for women.



The light grey line indicates healthy aghhers (score of 13-14),the middle grey line intermediate agers (score of 11-12), and the dark grey line poor agers (score of 0-10).
The hazard ratios for age-adjusted model 1, for healthy and intermediate ageing, compared to poor ageing, were 0.42 (95%CI: 0.34 to 0.52) and 0.63 (95%CI: 0.53 to 0.74) for men, and 0.44 (95%CI: 0.36 to 0.54) and 0.70 (95%CI: 0.61 to 0.82) for women, respectively.
Cum survival=cumulative survival.

The survival analysis results remained similar to the previous categorization based on tertiles of HAS (*Supplemental Figures 2A and 2B*).
Finally, in complete case analyses and in analyses excluding people who died within the first 3 years of follow-up, the direction, magnitude, and significance of the association between continuous HAS and mortality remained the same.

DISCUSSION

Considering the growing importance of healthy ageing as a key public health challenge, we developed a healthy ageing score consisting of 7 biopsychosocial domains in the population-based Rotterdam Study. Overall, we found that the HAS was lower in women in all age categories. With regard to the specific domains, more men had multimorbidity (i.e. more than 1 chronic disease) compared to women, whereas women had worse mental health, more pain, more disability, and a lower quality of life compared to men. The HAS declined with increasing age, albeit slightly steeper in women. Additionally, a higher HAS was strongly associated with lower mortality in both genders. Whereas the strength of this effect was stable across age groups in men, the association was less strong in older women compared to younger women.

Methodological considerations

This study developed a HAS in a large population-based sample and explored age and gender differences in great detail. Strengths of our study include the large sample size, availability of detailed information which led to a comprehensive definition for HAS; incorporating physiological constructs, social support, as well as quality of life. The latter two have proven to be of particular importance in the elderly, as their subjective attitudes towards health may differ significantly from what is measured objectively.[17] Additionally, the multidimensionality of the score allowed us to capture other aspects of healthy ageing that have not been explicitly included in the score. For example, we would expect to capture the burden of osteoporosis and fractures in the domains of pain and physical function. Another strength of our study is that our defined healthy ageing score is an interesting tool for clinical settings, for several reasons. Importantly, our defined healthy ageing score is relatively easy and inexpensive to measure, since all domains can be measured using questionnaires. In addition, the 0-14 continuous scale makes it easier to detect changes in healthy ageing over time, compared to a conventional dichotomous successful vs non-successful ageing approach. Finally, the comprehensive definition of HAS allows for directed interventions targeting the domains that require attention.

Besides these strengths, the limitations also merit careful consideration. Unhealthy persons were less likely to be included in the current study, compared to the more healthy agers. Therefore, as inherent to all cohort studies, the possibility of health selection bias cannot be ruled out. Moreover, nearly all participants were of Caucasian descent. Therefore,

the generalisability of our findings may be hampered. Furthermore, severity of disease was not included as a separate domain. Although this could have been captured, to some extent, in the other domains of the HAS, we cannot rule out that this might have led to an underestimation of the levels of morbidity.

Furthermore, given that there is no consensus for the definition of healthy ageing or uniform measurement guidelines, the cut-offs used within some of the domains and for the HAS were arbitrary (i.e. a score of 0, 1, or 2). Although we could have lost information by categorizing continuous measures, such as the Mini Mental State Examination for the domain of cognitive function, it prevented the use of complex statistical modelling strategies. Hence, the HAS in its current form allows for straightforward interpretation from a clinical perspective.

Each domain was given an equal weight in the total score. Although we can argue that there is sufficient evidence from literature for inclusion of each of these domains, we cannot judge whether or not all should receive the same weight. If one would want to assess weights of specific domains, a multivariable prediction rule should be created, with an outcome that can serve as an adequate gold standard measure for healthy ageing. Since there are different working definitions of healthy ageing, and various perspectives to which underlying construct is being measured, there is no consensus on the best gold standard for healthy ageing measurement tools. Furthermore, the most appropriate gold standard may depend on the objectives and context in which healthy ageing is measured. A possible gold standard could be resilience, and is the opposite of vulnerability: the underlying construct of frailty.[10 27 28] How much the concepts of healthy ageing and frailty overlap, remains to be elucidated.[29] Others have proposed vitality[30] or positive health (e.g. flourishing)[31] as underlying constructs of healthy ageing. In our study, we did not create such multivariable prediction rule. However, we did assess that the correlation between the domains did not exceed 0.55. Hence, this provides assurance that the overlap between the domains was sufficiently small.

Results in relation to other studies

Both men and women scored high on the healthy ageing score, i.e. a mean score of above 10 on a scale from 0-14. Approximately one third to half of the participants were classified as healthy agers, depending on the cut-off used. This finding is in line with a review summarizing 28 studies, in which the mean reported proportion of successful agers was 35.8% (SD 19.8).[16] In contrast, the large variation in measurement scales among studies resulted in large variation in proportion of successful agers in a second review that varied between 1 and 90%.[15]

Gender differences in healthy ageing

We observed numerous gender differences in HAS at all ages. Women had a lower proportion of healthy agers compared to men, which was in line with a similar study from Assmann and colleagues.[18] Despite women living longer than men, their extended life expectancy was accompanied by poorer scores in more domains, including worse mental health, more pain,

and more disability. Given the weaker relation of these domains with mortality, this may also explain why in older women the association between the HAS and mortality became weaker. These findings are in line with the theory of the 'male-female disability-survival paradox', which describes that women live longer than men but with more disability.[32 33] To explain this paradox several explanations have been proposed. Among others, sex-specific gene expression and differential effects of sex hormones can be related to this paradox.[34] Another explanation encompasses behavioural differences between the sexes, in such that men and women differ with regard to their symptom perception and attribution,[35] patient delay for consulting health care professionals,[35] and over reporting of worse health outcomes in women.[33 36] Also, less pathognomonic symptom presentation in women may lead to diagnostic delays and less timely treatment initiation, which could result in more severe consequences in terms of long-term disability.[34] It may also be possible that men have greater severity of disease, resulting in higher mortality.[33]

CONCLUSIONS

In the current study, we developed a comprehensive score for healthy ageing in a population-based study. The score included biological, psychological and social domains, most of which were easy and inexpensive to measure with questionnaires. We found that levels of the HAS in this elderly population were high, and that considerable gender and age differences occurred. These included lower levels of HAS and steeper decline across age categories in women and the differential importance of the different health domains between the sexes.

Future research is needed to further understand which factors are associated with healthy ageing and which interventions are effective for maintaining, improving, and recovering healthy ageing. In this regard, a gender-sensitive approach needs to be adopted. Additionally, more research is needed to assess changes in healthy ageing over time, within individuals and between populations. From a conceptual perspective, a better understanding of which gold standard underlying constructs should be used, could aid the establishment of a strong contemporary field of healthy ageing research.

The importance of keeping people healthy throughout their life course is evident, particularly when taking into account that our population is ageing. This study adds to the body of research by expanding the existing theoretical frameworks and incorporating experiences from other operational definitions, to define a practical application. The findings of our study have implications for researchers, clinicians, and policy makers, for all of whom a gender-sensitive perspective is essential.[19] For researchers, this is an interesting tool to adopt given its theoretical and experience-based foundation. Clinicians could benefit from monitoring healthy ageing in their patients over time. Finally, the measurement of healthy ageing in populations could help policy makers to allocate funds to keeping people healthy.

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Author contributions

Study concept and design: LJ, OHF, MK
Acquisition, analysis, or interpretation of data: LJ, JDS, NSE, SKLD, MLPP, SS, LL, GGB, BHS, HT, MAI, JSEL, OHF, MK
Drafting of the manuscript: LJ
Critical revision of the manuscript for important intellectual content: LJ, JDS, NSE, SKLD, MLPP, SS, LL, GGB, BHS, HT, MAI, JSEL, OHF, MK
Statistical analyses: LJ
Administrative, technical, or material support: not applicable
Study supervision: JSEL, OHF, MK
All authors approved the final version of the manuscript.

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Disclosures

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Supplemental material

Supplemental material related to this article can be found online at *http://dx.doi.org/10.1016/j.jamda.2016.11.021.*

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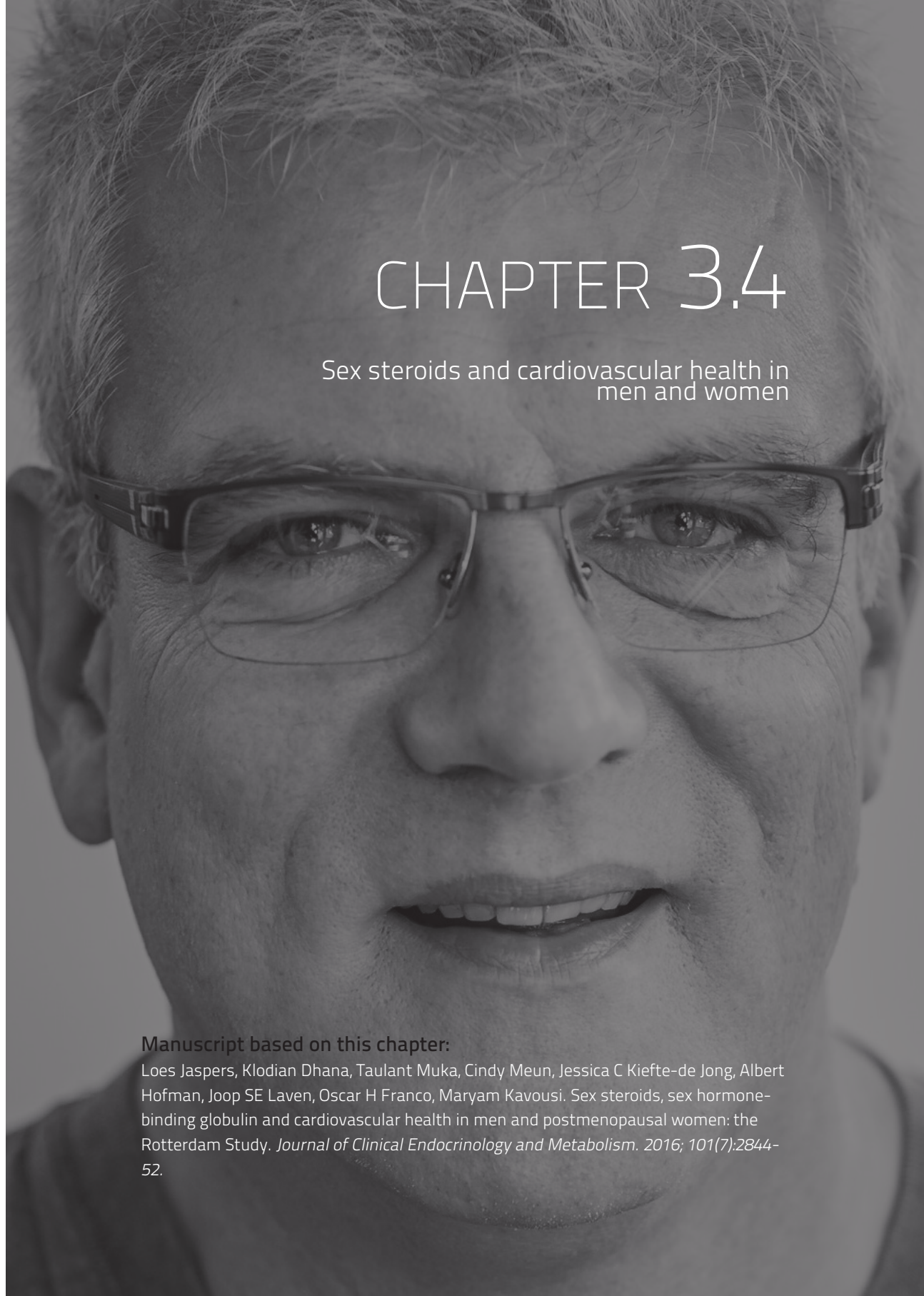


CHAPTER 3.4

Sex steroids and cardiovascular health in men and women

Manuscript based on this chapter:

Loes Jaspers, Klodian Dhana, Taulant Muka, Cindy Meun, Jessica C Kiefte-de Jong, Albert Hofman, Joop SE Laven, Oscar H Franco, Maryam Kavousi. Sex steroids, sex hormone-binding globulin and cardiovascular health in men and postmenopausal women: the Rotterdam Study. *Journal of Clinical Endocrinology and Metabolism. 2016; 101(7):2844-52.*

ABSTRACT

Background:

The concept of cardiovascular health (CVH) was recently introduced. Sex steroids and sex hormone-binding globulin (SHBG) influence different health domains, but no studies assessed their role in CVH.

Objective:

To assess the association between estradiol (E_2), testosterone (T), SHBG, and free androgen index (FAI) with CVH.

Design, setting, and participants:

Analyses included 1647 men (68.6 years) and 1564 naturally-postmenopausal women (69.6 years) with available data on sex steroids and CVH from the population-based Rotterdam Study.

Main exposure measures:

E_2, T, SHBG, and FAI.

Main outcome measures:

To define CVH, 7 metrics including 3 health factors (total cholesterol, fasting glucose and blood pressure) and 4 health behaviours (physical activity, smoking, body mass index and diet) were adopted. Three category levels of each metric were added up to a total score ranged 0-14. Logistic regression was performed to explore the association between E_2, T, SHBG, and FAI and optimal cardiovascular health (OCH, score 11-14).

Results:

OCH was reached by 153 men (9.3%) and 162 women (10.4%). The prevalence of OCH was higher in the lowest tertile of E_2 (38.9%), and of T (43.8%), and the highest tertile of SHBG (48.1%) in women, and the highest tertile of T (43.1%) and SHBG (47.1%) in men. After adjustment for confounders, OCH was associated with lower T (OR (95%CI): 0.69 (0.48 to 1.00)) and lower FAI (0.43 (0.32 to 0.57)) and higher levels of SHBG (4.55 (2.99 to 6.94)) among women and with higher levels of SHBG (2.56 (1.45 to 4.4)) in men.

Conclusions:

OCH was associated with sex steroids and with SHBG in both men and women. The complexity and temporality of the interrelation between sex steroids, SHBG, and CVH requires further investigation.

Keywords:

sex steroids, sex hormone-binding globulin, cardiovascular diseases, epidemiology

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide.[1 2] To outline new directions for research and to advocate clinical and public health programs for health promotion and disease prevention, in 2010 the American Heart Association (AHA) introduced the concept of cardiovascular health.[3] This new concept defines health as a broader construct than merely the absence of clinically apparent disease and is based on the levels that span the entire range of seven health factors and behaviours; including cholesterol, glucose, blood pressure, physical activity, smoking status, body mass index, and diet.[3]

With the use of cut-offs for levels of health factors and behaviours that are all literature-based or originating from clinical practice guidelines, the AHA defines the cardiovascular health status as poor, intermediate, or ideal.[3] Ideal cardiovascular health (ICH) is defined as having ideal levels of 3 health factors (total cholesterol <200 mg/dL, fasting plasma glucose <100 mg/dL, and blood pressure <120 / <80 mm Hg) and 4 health behaviours (75-150 minutes of moderate and/or vigorous physical activity, non-smoking, body mass index <25 kg/m^2, and a healthy diet).[3]

ICH has been shown to be related to less severe subclinical atherosclerosis,[4-6] lower incidence of CVD and lower cardiovascular mortality.[6-10] However, the applicability and relevance of cardiovascular health metrics extend beyond the cardiovascular system. Ideal cardiovascular health is also related to better cognition,[11] better psychological status,[12] lower cancer risk,[13] more favourable overall functional status,[14] and lower all-cause mortality.[9 10]

Sex steroids, such as estradiol (E_2) and testosterone (T), and sex hormone-binding globulin (SHBG), influence individual cardiovascular risk factors and cardiovascular morbidity and mortality,[15-18] and differences between men and women have been reported.[19] The pivotal role of sex steroids and SHBG in bodily systems, among which the cardiovascular system, makes them a promising interventional target. Thus far, sex steroids and SHBG have been mostly related to the single cardiovascular risk factors and the presence or absence of CVD and its related comorbidities.[15 16] Nevertheless, large population-based samples, using gold standard measures of sex steroids and SHBG together with concurrent analyses in men and women are lacking. Using the recent AHA concept of cardiovascular health, we aimed to assess the association between sex steroids (including E_2 and T), SHBG and free androgen index (FAI) with overall cardiovascular health among men and postmenopausal women from a large population-based cohort study.

METHODS

Study population

The study was embedded within the Rotterdam Study (RS), a prospective, population-based cohort study among subjects 55 years and older in the municipality of Rotterdam, the Netherlands. The rationale and study design have been described in detail elsewhere.[20] The baseline examination was completed between 1990 and 1993 (RS-I). The cohort was extended in 2000, to include all inhabitants who had become 55 years of age or moved into the research area after the start of the study (RS-II).

The present study included 1647 men and 1564 postmenopausal women from the third visit of RS-I (1997-1999) and the baseline visit of RS-II (2000-2001) with written informed consent and available sex steroid and SHBG measurements and cardiovascular health metrics. Women with surgical menopause or women who reported ever using female steroids were excluded from the analyses. An overview of the study participant selection can be found in the flowchart (*Figure 1*). The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC and by the Ministry of Health, Welfare and Sport of the Netherlands, implementing the Wet Bevolkingsonderzoek: ERGO (Population Studies Act: Rotterdam Study). All participants provided written informed consent to participate in the study and to obtain information from their treating physicians.

Measurements of E_2, T, SHBG, and FAI

All blood samples were drawn in the morning (≤ 11:00 am) and were fasting.

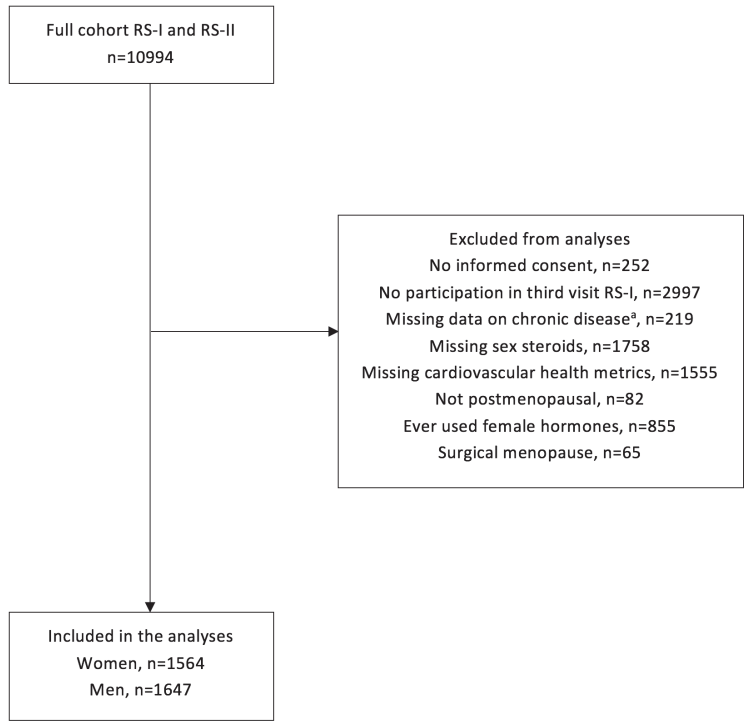
Estradiol levels were measured with a radioimmunoassay and SHBG with the Immulite platform (Diagnostics Products Corporation Breda, the Netherlands). The corresponding intra- and interassay coefficients of variation with lower limit of detection (LLOD) of the assays were <11%, <11% and 18.35 pmol/L for E_2 and <4%, <5% and 0.02 nmol/L for SHBG. Serum levels of T were measured with liquid chromatography-tandem mass spectrometry (LC-MS/MS), with a corresponding interassay of <5% and a lower limit of quantification (LLOQ) of 0.07 nmol/L. The FAI was calculated as (T/SHBG)*100 and only in women, since this measure performs poorly in men, and is considered a surrogate marker for free testosterone levels.[21]

Optimal cardiovascular health

The 7 metrics of cardiovascular health included 3 health factors (total cholesterol, glucose and blood pressure) and 4 health behaviours (body mass index (BMI), diet, smoking, physical activity)[3]. A detailed description of the application of the 7 metrics to the participants of the Rotterdam Study can be found in the *Supplemental Methods Section*. We used the AHA definitions of poor, intermediate, and ideal categories for each of the 7 metrics. The thresholds for these categories were based on data available from existing guidelines and from reviews of the literature.[3]

For each metric, a participant received 0 points if that metric fell into the poor category (i.e. BMI ≥30), 1 point for the intermediate category (i.e. BMI = 25-29.9) or 2 points for the ideal category (i.e. BMI <25). Every metric had the same weight. Therefore, as there are 7 metrics in total, a maximum score of 14 could be reached. Participants with prevalent CVD (including CHD, stroke, and heart failure) were not excluded from the analyses; instead their metric scores were subtracted by 1, resulting in a maximum total cardiovascular health score of 7 for these subjects.[3] For the metrics total cholesterol, blood pressure, and fasting plasma glucose, being treated for hypercholesterolemia, hypertension or diabetes, was accounted for by assigning a lower score on that metric to the participant (e.g. moving from the ideal to the intermediate category).[3] None of the participants had ideal cardiovascular health, i.e. a score of 14. Therefore, for statistical analyses purposes, the total cardiovascular health score was dichotomized into 2 groups: optimal cardiovascular health (OCH, score of 11-14) versus non-optimal (non-OCH, score of 0-10).

Figure 1. Flowchart for selection of study participants.



[a] Chronic diseases include diabetes mellitus, cardiovascular disease, chronic obstructive pulmonary disorder, and cancer.
RS=Rotterdam Study.

Statistical analyses

Participant characteristics were described using means (standard deviations) and proportions. The prevalence of OCH in gender-specific tertiles of E_2, T, SHBG, and FAI was determined. Thereafter, statistical significant differences between these prevalences were assessed using a Chi square test.

To assess the independent relationship between the exposures E_2, T, SHBG, and FAI with the outcome OCH, logistic regression was used. Analyses were performed separately for men and women. Because of skewed distributions, E_2, T, SHBG, and FAI were transformed to a natural logarithmic scale. Per exposure 3 models were created. The covariates were selected based on their association with both E_2, T, SHBG, or FAI and cardiovascular health. Model 1 was adjusted for age and for years since menopause (only in women). Model 2, was adjusted for age, years since menopause (only in women), cohort (RS-I vs RS-II), ethnicity (Caucasian vs. non-Caucasian), marital status (married, never married/divorced, widowed), chronic disease including CVD, DM, cancer and chronic obstructive pulmonary disorder (absent vs present), education (continuous), and other sex steroids. In model 3, we additionally adjusted model 2 for waist-hip ratio. Model 3 could be considered a conservative model, since body fat most likely intermediates in the association between E_2, T, SHBG, and FAI and cardiometabolic factors, for instance via the direct increase of androgen production (both via the enzyme 17beta-hydroxysteroid dehydrogenase in adipose tissue as well as via stimulation of androgen production in the ovaries), and the stimulation of insulin and insulin-like growth factor resulting in the inhibition of SHBG production in the liver.[22-25]

Estradiol levels below 18.35 pmol/L were under the detection limit of the immunoassay used, which led to a truncated distribution, particularly in women. Therefore, we checked whether the association for tertiles of E_2 and OCH in women would show the same trend as the continuous approach.

In order to further explore the role of the health behaviours and the health factors, the total cardiovascular health score was separated into a cardiovascular behaviour (optimal score 7-8) and a cardiovascular factor score (optimal score 6-8) and the same models as described above were created.

In sensitivity analyses we restricted the analyses to the healthy population, excluding men and women with prevalent chronic diseases including CVD, chronic obstructive pulmonary disorder (COPD), and cancer.

All analyses were performed using IBM SPSS Statistics version 21.0. Associations were considered statistically significant at a p-value < 0.05. In a more conservative approach and to take into account multiple testing, we applied a conservative Bonferroni corrected p-value of p<0.0125 for 4 tests (E_2, T, SHBG, and FAI), since these exposures are interrelated.

RESULTS

Of the study population, nearly all were from Caucasian descent and 48.7% were women. The mean age of the study population was 68.6 years (SD 7.5) and 69.6 years (SD 8.0) in men and women respectively. Women were on average 20.4 years (SD 9.4) after menopause. An overview of the study characteristics, including cardiovascular health metrics as well as sex steroids and SHBG can be found in *Table 1*.

None of the participants adhered to the definition of ICH (i.e. a total score of 14). Optimal cardiovascular health (OCH, score of 11-14) was reached by 153 men (9.3%) and 162 women (10.4%).

In men, the prevalence of OCH was non-significantly higher in the middle tertile of estradiol (p for the difference: 0.080) (*Figure 2A*). In women, the prevalence of OCH (38.9%) was slightly higher in the lowest tertile of E_2 but the differences were not statistically significant (Figure 2A). For T, a differential trend was found between men and women (*Figure 2B*). The highest prevalence of OCH (43.1%) was found for the highest levels of T (tertile 3) in men, whereas in women the highest prevalence (43.8%) was found for the lowest levels of T (tertile 1). For both men and women, prevalence of OCH was the highest for high levels of SHBG (47.1% for men and 48.1% in women) (*Figure 2C*). Prevalence of OCH was significantly higher (52.5%) in the lowest levels of FAI (tertile 1) in women (*Figure 2D*).

In *Table 2* the associations between per unit increase natural log transformed E_2, T, SHBG, and FAI with OCH can be found, expressed in odds ratios (OR) and 95% confidence intervals (95%CI). Optimal cardiovascular health was associated with lower levels of E_2 in women (OR (95%CI): 0.66 (0.48 to 0.89)) and with higher levels of T in men (OR (95%CI): 2.33 (1.43 to 3.80)) in model 1, but did not remain statistically significant in model 2 (after adjustment for all potential confounders). For women, the direction of the observed effect remained the same for categorized E_2, indicating that the observed effect is not driven by the detection limit of the E_2 assay. Lower T was significantly associated with OCH in model 2 for women (OR (95%CI): 0.69 (0.48 to 0.99)).

Furthermore, OCH was associated with higher levels of SHBG in both men and women in model 2 (OR (95%CI): 2.56 (1.45 to 4.49) for men and 4.55 (2.99 to 6.94) for women). In women, OCH was further associated with lower levels of T (OR (95%CI): 0.69 (0.48 to 1.00)) and FAI (OR (95%CI): 0.43 (0.32 to 0.57)). All associations mentioned above remained significant after applying a conservative Bonferroni correction for 4 tests, except the association between T and OCH in women. After additionally adjusting model 2 for waist-hip ratio in the conservative models (model 3), the magnitude of the associations between E_2, T, SHBG, and FAI with OCH attenuated. Nevertheless, the odds ratio of SHBG in men and SHBG and FAI in women remained statistically significant.

In sensitivity analyses, restricted to the healthy population, the association between E_2, T, SHBG, and FAI and OCH remained the same (*Supplemental Table 1)*. When splitting up the total cardiovascular health score into optimal behaviours and factors, the direction of the observed effects in men and women remained the same and the magnitude of

the effects remained similar. The significance of the associations for optimal factors was comparable to OCH. For optimal behaviours some differences in significance were observed; in men the association between T and optimal behaviours and in women the associations for T and E_2 with optimal behaviours remained significant in all models, which was not the case for OCH *(Supplemental Table 2*).

Table 1. Characteristics of the study population.

	Men, n=1647	Women, n=1564
General characteristics		
Age, years	68.6 (7.5)	69.6 (8.0)
Prevalent chronic disease, yes[a]	606 (36.8%)	346 (22.1%)
Waist-hip ratio	0.97 (0.93 to 1.01)	0.86 (0.81 to 0.93)
Ethnicity, Caucasian	1611 (97.8%)	1531 (97.9%)
Education		
Primary	147 (8.9%)	256 (16.4%)
Lower/intermediate or lower vocational	522 (31.7%)	837 (53.5%)
Intermediate vocational or higher general	640 (38.9%)	365 (23.3%)
Higher vocational or university	338 (20.5%)	106 (6.8%)
Marital status		
Married, living together	1424 (86.5%)	972 (62.1%)
Never married, divorced	91 (5.5%)	221 (14.1%)
Widowed	132 (8.0%)	371 (23.7%)
Health behaviours		
BMI, kg/m^2	26.5 (3.1)	27.2 (4.3)
Smoking		
Current	383 (23.3%)	247 (15.8%)
Former	16 (1.0%)	9 (0.6%)
Never	1248 (75.8%)	1308 (83.6%)
Diet		
Sodium intake, g/day	2192 (1900 to 2512)	2163 (1871 to 2486)
Wholegrain intake, g/day	128 (83 to 168)	117 (88 to 155)
Fish intake, g/week	73 (0.44 to 167)	69 (0.65 to 158)
Fruit & vegetable intake, g/day	372 (275 to 498)	445 (331 to 589)
SSB intake, g/week	34 (-0.50 to 479)	6 (1 to 290)
Physical activity		
Moderate and vigorous activity, min/week	885 (540 to 1350)	960 (630 to 1410)

Table 1. Continued

Health factors		
Diastolic blood pressure, mmHg	77.6 (11.4)	75.2 (10.7)
Systolic blood pressure, mmHg	143.3 (20.8)	142.3 (20.7)
Total cholesterol, mg/dl	213.8 (36.8)	233.4 (37.0)
Fasting blood glucose, mg/dl	108.1 (26.5)	103.4 (20.2)
Serum lipid lowering medication, yes	208 (12.6%)	185 (11.8%)
Antidiabetic therapy, yes	84 (5.1%)	51 (3.3%)
Blood pressure lowering medication, yes	345 (20.9%)	364 (23.3%)
E_2, T, SHBG, and FAI		
Estradiol, pmol/L	98.7 (76.1 to 125.8)	27.5 (18.4 to 51.8)
Testosterone, nmol/L	16.7 (13.1 to 20.9)	0.9 (0.6 to 1.2)
SHBG, nmol/L	46.5 (36.0 to 59.7)	60.2 (43.7 to 83.1)
Free androgen index	NA	1.4 (1.0 to 2.2)
Women-specific variables		
Age of menopause, years[b]	NA	49.1 (4.7)
Menopause type, natural menopause	NA	1305 (83.4%)
Years since menopause, years[b]	NA	20.4 (9.4)

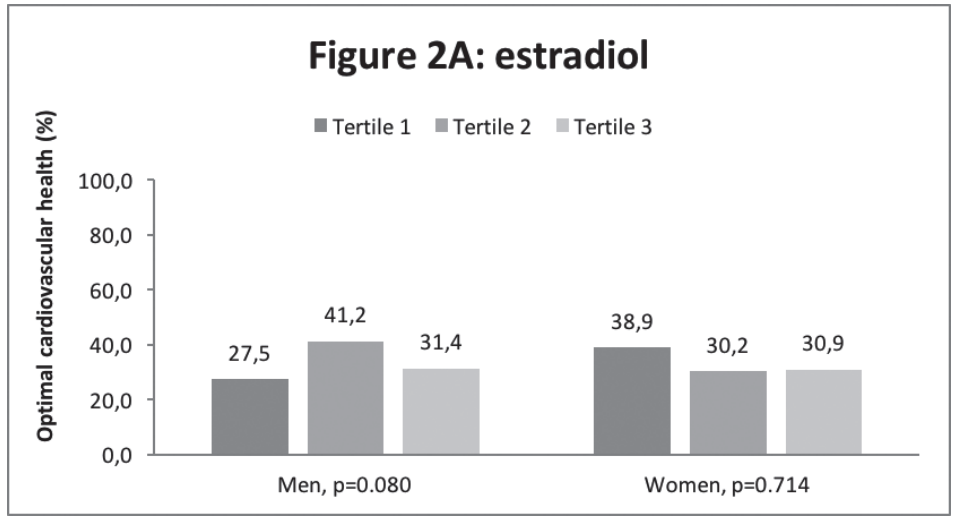
[a] Prevalent chronic disease consists of diabetes mellitus, cardiovascular disease, chronic obstructive pulmonary disorder, and cancer.
[b] Age of menopause was not available for all women, the presented value is based on 1551 women.
Values are reported as number (percentage) for categorical variables and mean (standard deviation) or median (27th-75th quartile) for continuous variables.
BMI=body mass index, E_2= estradiol, FAI=free androgen index, n=number, NA=not applicable, RS=Rotterdam Study, SHBG=sex hormone-binding globulin, SSB=sugar sweetened beverages, T=testosterone.

DISCUSSION

Overall, levels of sex steroids and SHBG were associated with cardiovascular health including factors and behaviours, irrespective of potential confounders. Optimal cardiovascular health was associated with lower levels of T and FAI and with higher SHBG levels in women. Among men, OCH was associated with higher SHBG levels. In our population, none of the participants had ideal cardiovascular health (i.e. a score of 14) and only one tenth had optimal cardiovascular health (i.e. a score of 11-14).

Cardiovascular health has been shown to be related to different risk factors and diseases of the cardiovascular system and its effects extend further to other health domains.[4-14] The marked low prevalence of ideal cardiovascular health in our study is similar to previously published reports.[6-10] Studies have shown that better cardiovascular health translates into lower risks for cardiovascular morbidity and mortality as well as all-

Figure 2A-D. Prevalence of optimal cardiovascular health across gender-specific tertiles of E_2, T, SHBG, and FAI.



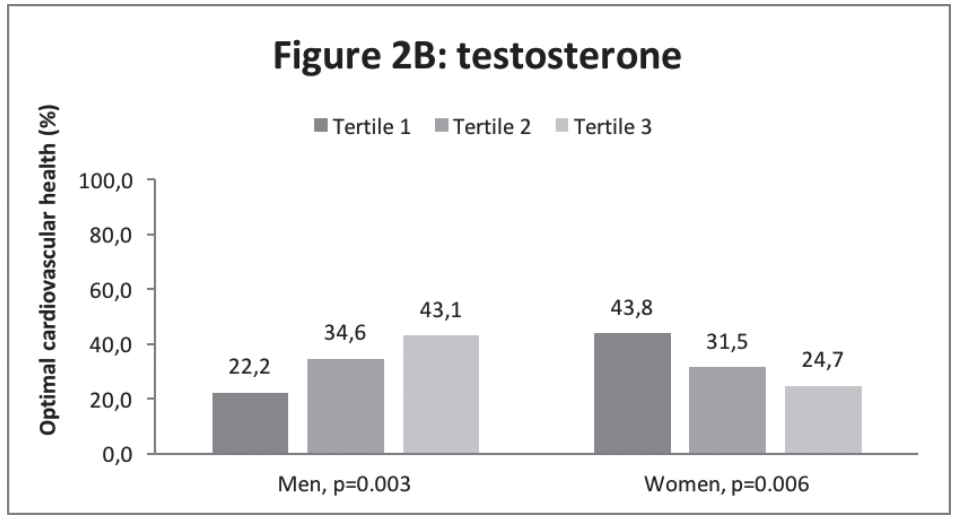
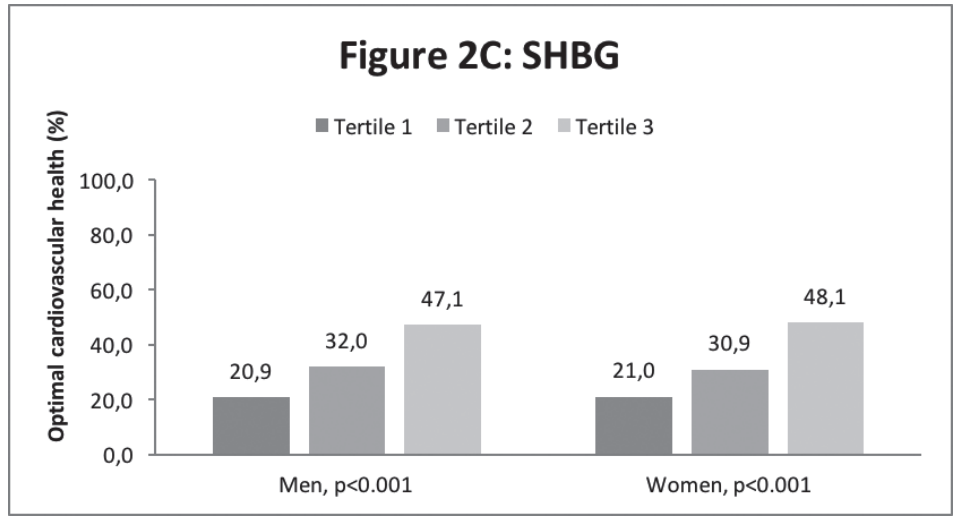
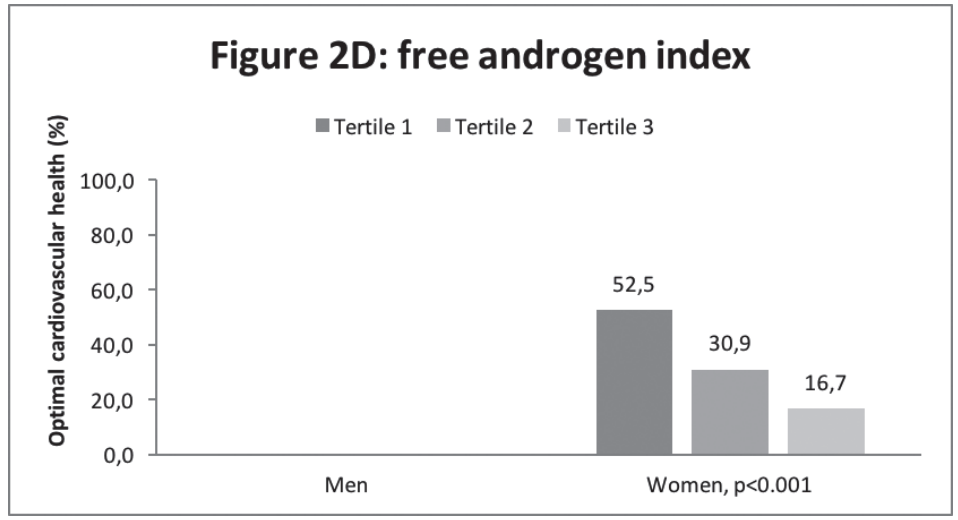


Figure 2A-D. Prevalence of optimal cardiovascular health across gender-specific tertiles of E_2, T, SHBG, and FAI.





E_2=estradiol, FAI=free androgen index, SHBG=sex steroid-binding globulin, T=testosterone.
The values of the tertiles are as follows:
Estradiol: men (18.4-83.8 / 83.9-115.7 / 115.8-365.5), women (18.4-18.4 / 18.5-42.3 / 42.4-320.0).
Testosterone: men (0.18-14.2 / 14.3-19.4 / 19.5-41.3), women (0.07-0.7 / 0.8-1.1 / 1.2-30.1).
SHBG: men (11.3-39.6 / 39.7-55.0 / 55.1-187.8), women (10.8-48.2 / 48.3-73.2 / 73.3-200.0).
FAI: women (0.05-1.1 / 1.2-1.9 / 2.0-38.0).

Table 2. The association between E_2, T, SHBG, and FAI with optimal cardiovascular health, stratified by gender.

	Men	Women
Estradiol	**OR (95%CI)**	**OR (95%CI)**
Model 1	1.33 (0.85 to 2.08)	**0.66 (0.48 to 0.89)***
Model 2	1.02 (0.59 to 1.76)	0.73 (0.50 to 1.07)
Model 3	1.21 (0.70 to 2.11)	0.75 (0.51 to 1.10)
Testosterone		
Model 1	**2.33 (1.43 to 3.80)***	0.81 (0.58 to 1.12)
Model 2	1.41 (0.81 to 2.45)	**0.69 (0.48 to 0.99)**
Model 3	1.25 (0.73 to 2.14)	0.70 (0.49 to 1.02)
SHBG		
Model 1	**3.10 (1.94 to 4.97)***	**4.25 (2.84 to 6.36)***
Model 2	**2.56 (1.45 to 4.49)***	**4.55 (2.99 to 6.94)***
Model 3	**2.12 (1.20 to 3.73)**	**3.55 (2.28 to 5.52)***
FAI		
Model 1	NA	**0.41 (0.31 to 0.54)***
Model 2	NA	**0.43 (0.32 to 0.57)***
Model 3	NA	**0.49 (0.36 to 0.67)***

Bold values indicate that the association is significant at p<0.05.
The asterisk * indicates that the association remains significant at a Bonferroni corrected p-value of p<0.0125 for 4 tests. The reported effect estimates are for 1 unit increase in log-transformed E_2, T, SHBG, and FAI.
Model 1: adjusted for age and for years since menopause (only in women).
Model 2: adjusted for age, years since menopause (only in women), cohort, ethnicity, education, marital status, prevalent cancer/COPD, and estradiol / testosterone / SHBG depending on the model.
Model 3: model 2 + waist-hip ratio.
CI=confidence interval, E_2=estradiol, FAI=free androgen index, NA=not applicable, OR=odds ratio, SHBG=sex hormone-binding globulin, T=testosterone.

cause mortality.[6-10] In our population, these previously reported findings were supported. Each unit increase in the cardiovascular health score was significantly associated with a 9% and 12% decrease in incident fatal and nonfatal cardiovascular disease in men and women, respectively (data not shown). For all-cause mortality this decrease in incidence was 7% in men and 9% in women (data not shown).

The importance of androgens and of SHBG with regard to the cardiovascular system in both men and women is progressively becoming apparent.[15 16 18 19] Sex steroids and SHBG have been shown to influence individual cardiovascular risk factors and cardiovascular morbidity and mortality.[15 16 18 19] To date, most studies have focused on the absence or presence of single cardiovascular risk factors or diseases. By adopting the AHA metrics for cardiovascular health we were able to provide a comprehensive overview of the association between sex steroids and SHBG with cardiovascular health in the general population and these associations differed in terms of magnitude and direction by type of exposure (i.e. E_2, T, SHBG, or FAI) and gender.

Androgens & SHBG

Higher levels of T were associated with optimal cardiovascular health among men. However, after adjusting for confounders these findings did not remain statistically significant. Low endogenous T has been linked to a less favourable cardiovascular risk profile (e.g. dyslipidemia, blood pressure, thrombosis, endothelial dysfunction), whereas its role in CVD and CVD mortality is modest.[16 17] The therapeutic effects of exogenous T have not been proven to be beneficial or have even been harmful with regard to the risk of CVD.[16 26]

In women, lower levels of T and FAI were associated with optimal cardiovascular health. An unfavourable cardiovascular risk profile, atherogenicity, and more severe atherosclerosis have been associated with higher levels of T and FAI, although the significance of these results was not consistent across studies and hard clinical endpoints such as CVD and mortality were scarce.[15 18 27-29]

The FAI is calculated from total T and SHBG and only validated in women.[21] It would be possible that the significance of FAI is driven by SHBG.[18] Indeed in our data, in contrast to total T, high levels of SHBG were strongly associated with OCH in women.

Estradiol

For estradiol, no significant associations were found between E_2 and optimal cardiovascular health in men. Women with OCH tended to have lower levels of E_2, but this association did not remain significant after adjustment for potential confounders. Although the direction of this association seems counterintuitive, a recent study showed the same direction of effect, i.e. higher E_2 levels were associated with stiffer vessels that were smaller in diameter in both men and women.[29] Furthermore, the risk of CHD and stroke were elevated at higher levels of E_2, although this effect was attenuated after adjustment for confounders.[27 30] In metabolic studies, focusing on glucose intolerance

and diabetes, a similar trend was found.[31-33]

To date, it remains unclear which exact mechanisms underlie the relation between low E_2 and optimal cardiovascular health. However, several potential mechanisms have been described. Visceral adiposity, which is associated with atherogenic dyslipidemia, insulin resistance/diabetes, and inflammation, is suggested to increase E_2 levels via two pathways. Firstly, adiposity is negatively correlated with SHBG, which in turn leads to a higher fraction of bioactive E_2. Secondly, central adiposity increases aromatase activity and therefore the conversion of T into E_2.[34] Higher levels of E_2 have been shown to be more strongly associated with atherothrombotic stroke in older postmenopausal women who had greater central adiposity.[30] In our study, adjusting for waist-hip ratio in our conservative models led to an attenuation in the observed associations for all exposures, although the association between SHBG and FAI with OCH in women and SHBG and OCH in men remained significant, suggesting that body fat may not completely explain the relation between E_2, T, SHBG, and FAI and OCH.

Complexity of the role of sex steroids and SHBG in cardiometabolic health

Considering the complexity of the interactions and associations, which might further occur differently by gender, findings regarding the associations between sex steroids and SHBG and cardiovascular health should nevertheless be interpreted with caution. A point of notion for both men and women is the difference in the interpretation of results for free T versus total T with regard to cardiovascular endpoints.[16] Although the magnitude of the effect for both T measurement types is similar, each could reflect a different effect.[35] As shown in diabetes research, the longitudinal relation between free T and incident DM implies a direct sex steroid effect; whereas total T may in fact reflect the association between low SHBG and diabetes.[36 37] SHBG could be related to DM via a direct causal pathway or indirectly via insulin resistance.[15 16 36 38] Genetic studies have shown that polymorphisms in the SHBG gene are associated with a higher risk of diabetes, suggesting the existence of a direct pathway.[36 39 40] In addition, it has been suggested that the role of SHBG in the pathophysiology of insulin resistance and diabetes, extends beyond the binding and transport of sex steroids.[41-43] Studies have consistently shown that lower levels of SHBG are independently associated with higher insulin resistance and a higher risk of diabetes, implying that SHBG may be an important metabolic marker.[41-44] Furthermore, insulin sensitivity is associated with systemic inflammation, which has been shown to be related to CVD.[16] Indeed, in our data for both men and women we found a strong association between high SHBG levels and optimal cardiovascular health, that were independent from estradiol and testosterone, further emphasizing the importance of SHBG in the cardiometabolic system.

A second issue that warrants attention in all research focusing on E_2, T, SHBG, and FAI and cardiometabolic health is the fact that they are all interrelated. Cholesterol (one of the seven metrics of cardiovascular health) is a precursor of T, T can be aromatized into E_2 or reduced into dihydrotestosterone locally in cardiovascular tissues, and the

activity of androgens in its turn may depend on the levels of estrogen.[16 19 45] Furthermore, SHBG and other binding proteins play a key role in the activity of sex steroids and SHBG levels strongly depend on adiposity levels.[34 46] Therefore, it remains elusive whether the observed associations reflect a true relation or an underlying unobserved process.

Strengths and limitations

An important strength of our study is the availability of a large representative population-based sample with detailed information on the cardiometabolic profile for each individual. Furthermore, androgens were measured with LC-MS/MS, which is currently considered the gold standard method.[21 47] Our study is the first to focus on the association of E_2, T, SHBG, and FAI with the new concept of cardiovascular health, instead of merely the presence or absence of cardiovascular risk or disease. Good cardiovascular health has been related to optimal health in other domains such as better cognition,[11] better psychological status,[12] lower cancer risk,[13] more favourable overall functional status,[14] and lower all-cause mortality.[9 10] Therefore, the implications of the association between E_2, T, SHBG, and FAI and cardiovascular health may extend beyond the cardiovascular system. Given the increasing number of studies describing positive effects regarding the combination of several ideal health factors and behaviours for CVD free survival, overall (healthy) longevity, quality of life, and the subsequent reduction in health care costs, the overall cardiovascular health approach, in contrast to the individual risk factor approach, comprises growing clinical relevance.[3]

However, the limitations of our study also merit attention. Firstly, the cross-sectional design does not allow us to address the temporality of the observed associations. Therefore, we cannot draw any conclusions with regard to the causality of the observations. Nevertheless, the predefined definition of cardiovascular health, which includes both health factors and behaviours, made the application of a longitudinal study design unfeasible, for we would not expect E_2, T, SHBG, and FAI to directly predict health behaviours such as physical activity or smoking habits. However, indirect pathways have been described. Studies suggest that the menopausal transition is accompanied by a decrease in energy expenditure (mainly due lower physical activity levels), a decrease in food intake, and an increased appetite.[48 49] Furthermore, health behaviours can also affect levels of E_2, T, SHBG, and FAI, for example a healthy diet and exercise can decrease estradiol levels in postmenopausal women,[50] and lifestyle factors (e.g. smoking, diet, and physical activity) are associated with SHBG and T changes in men.[51 52] The levels of E_2, T, SHBG, and FAI might also be affected by changes in bodyweight. A study conducted by Wildman and colleagues suggests a unidirectional relation between body weight and sex steroids and SHBG, such that changes in body weight lead to changes in testosterone and SHBG. The relation between body weight and estradiol was bidirectional, although the associations in the direction of body weight predicting levels of estradiol were stronger than the reverse.[53]

Secondly, all metrics received the same weight (i.e. a score of 0, 1 or 2), since the definition of cardiovascular health does not prioritize any metric above the others.[3] In order to give insight in any differential effect of E_2, T, SHBG, and FAI on health factors and behaviours, a sensitivity analysis separating the two was performed and is provided in the supplementary material. Thirdly, we performed several number of tests. However, in order to take into account multiple testing, a conservative Bonferroni correction was applied which did not materially change the significance of our findings. Free T levels were not measured directly in the blood and therefore have to be interpreted with caution. Nevertheless, free T levels in this study were derived from the ratio of T to SHBG, which is considered a precise proxy for bioavailable T.[54] Finally, E_2 was measured using an immunoassay with a detection limit of 18.35 pmol/L, which is considered suboptimal particularly in postmenopausal women. However, the direction of the observed effect remained the same whilst analysing E_2 continuously and categorically.

CONCLUSIONS

In summary levels of sex steroids and SHBG were associated with optimal cardiovascular health. Optimal cardiovascular health was associated with lower levels of T and FAI and with higher SHBG levels in women. Among men, OCH was associated with higher SHBG levels. After additional adjustment for waist-hip ratio, the effect sizes of E_2, T, SHBG, and FAI in both men and women attenuated, although they remained significant for FAI and SHBG in women and for SHBG in men.

Using the concept of cardiovascular health, instead of merely the presence or absence of disease or focus on separate cardiovascular risk factors, allowed us to assess the role of E_2, T, SHBG, and FAI in the cardiovascular system in a comprehensive manner and the implications may extend beyond the cardiovascular system to other health domains.

To facilitate the development of preventative and treatment strategies, the complexity and temporality of the interrelation between E_2, T, SHBG, and FAI and the cardiometabolic profile, and the role of body fat distribution in particular, warrants further investigation.

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Disclosures

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Supplemental material

Supplemental material related to this article can be found online at *http://press.endocrine.org/doi/suppl/10.1210/jc.2016-1435.*

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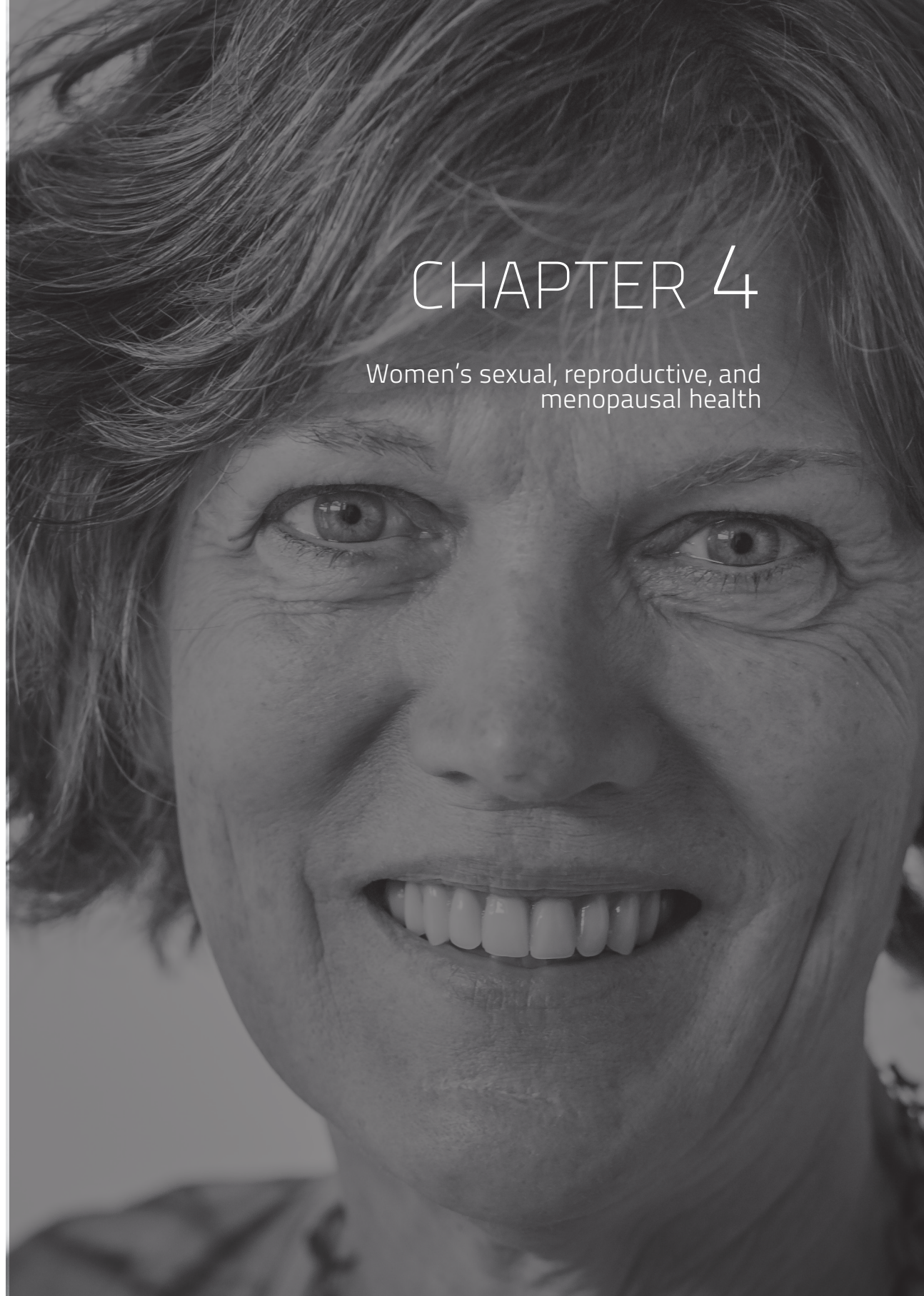
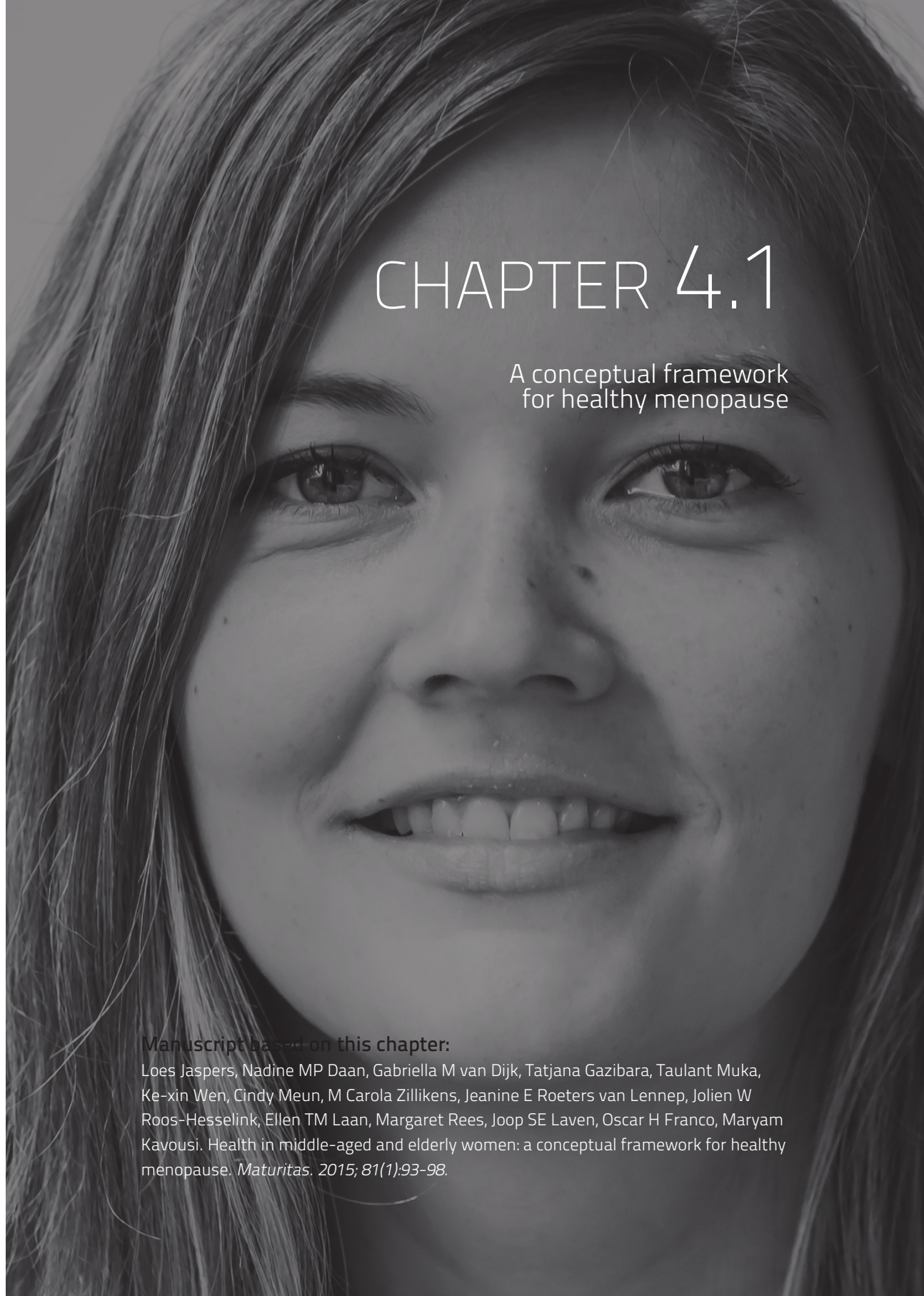
CHAPTER 4

Women's sexual, reproductive, and menopausal health





CHAPTER 4.1

A conceptual framework for healthy menopause

Manuscript based on this chapter:

Loes Jaspers, Nadine MP Daan, Gabriella M van Dijk, Tatjana Gazibara, Taulant Muka, Ke-xin Wen, Cindy Meun, M Carola Zillikens, Jeanine E Roeters van Lennep, Jolien W Roos-Hesselink, Ellen TM Laan, Margaret Rees, Joop SE Laven, Oscar H Franco, Maryam Kavousi. Health in middle-aged and elderly women: a conceptual framework for healthy menopause. *Maturitas. 2015; 81(1):93-98.*

ABSTRACT

Middle-aged and elderly women constitute a large and growing proportion of the population. The peri and postmenopausal period constitutes a challenging transition time for women's health, and menopausal health is a crucial aspect in healthy and successful ageing. Currently, no framework for the concept of healthy menopause exists, despite its recognized importance. Therefore, we aimed to: (i) characterize healthy menopause; (ii) identify aspects that contribute to it; and (iii) explore potential approaches to measure it.
We propose healthy menopause as a dynamic state, following the permanent loss of ovarian function, which is characterized by self-perceived satisfactory physical, psychological and social functioning, incorporating disease and disability, allowing the attainment of a woman's desired ability to adapt and capacity to self-manage. The concept of healthy menopause applies to all women from the moment they enter the menopausal transition, up until they reach early and late postmenopause and includes women with spontaneous, iatrogenic, and premature menopause.
This conceptualization can be considered as a further step in the maintenance and improvement of health in menopausal women from different perspectives, foremost the woman's own perspective, followed by the clinical, public health, and societal perspectives, and can be seen as a further step in delineating lines for future research. Furthermore, it could facilitate the improvement of adequate preventive and treatment strategies, guide scientific efforts, and aid education and communication to health care practitioners and the general public, allowing women the achievement of their potential and the fulfillment of their fundamental role in society.

Keywords:

health, menopause, ageing, conceptual framework, measurement

Pushing the boundaries of life

Our population is ageing. As a result of improvements in health care and prevention accompanied by declining fertility rates, the proportion of people above 60 years of age is increasing.[1 2] This is particularly the case for women, as their life expectancy is 6-8 years longer than for men.[1] Despite the advantages for women in terms of life expectancy, women tend to live longer suffering disease and disability: men die quicker, women get sicker.[3 4] Disease and disability in women has been related with a key transitional phase women experience in midlife: menopause. The menopausal transition demarks dramatic changes at the hormonal, physiological, and metabolic level.[5] These alterations, accompanied by burdensome life experiences and lifestyle changes, lead to an increased risk of chronic noncommunicable disorders among women.[6] The peri and postmenopausal period constitutes a challenging transition time for women's health, and good menopausal health is a crucial aspect in healthy and successful ageing, carrying substantial societal benefits.[5 6]

Menopause and the health related aspects of menopause have been intensively studied.[7 8] Nevertheless, a comprehensive conceptualization of healthy menopause and its entailment remains unclear. Until now no studies have characterized healthy menopause or have come up with a framework to describe the concept of menopausal health. Therefore we aimed to: (i) characterize healthy menopause; (ii) identify aspects that contribute to healthy menopause; and (iii) explore potential approaches to measure healthy menopause.

Health…the holy grail?

Good health can be considered both an individual's fundamental right as well as a resource for individuals to be able to fulfil their personal, social, and economic roles in society.[9] Therefore, many have attempted to define it. The best known definition of health was formulated by the World Health Organization in 1948: "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity".[10] The applicability of this definition is limited and has been challenged by the observed shift from acute to chronic disease over the last decades as the literal implementation of the definition would designate all chronically diseased as permanently ill. With improved detection, diagnosis, treatment, and survival, levels of health and the possibility of being characterized as healthy diminishes even further. Additionally, "complete health and wellbeing" although a commendable goal, is also hard to achieve and challenging to operationalize.[11 12]

This could be a reason why past and current health research does not focus on health but rather on risk factors, diseases, and mortality. This approach to health research might limit our understanding of the overall effect of factors that are involved in the dynamics of obtaining, regaining, and maintaining health. Furthermore, a more general focus on health as a multidimensional state could facilitate prevention and treatment strategies.[13]

Contemporary approaches to health

The conceptualization of health has been influenced by sociologist Aaron Antonovsky, who developed the theory of salutogenesis, i.e. the origin of health characterized by the relation between health, stress and coping, and which can be seen as the complement of pathogenesis.[14] The theory rejects the current separation of health and illness and positions individuals along the "health-ease – dis-ease continuum". This complementary approach to health and disease is also reflected in the classification systems of the WHO, including the International Classification of Diseases and the International Classification of Functioning, Disability and Health.[15 16]

A more recent definition of health is given by Bircher and describes health as a balance between individual potential and faced demands: "Health is a dynamic state of wellbeing characterized by a physical, mental and social potential, which satisfies the demands of a life commensurate with age, culture, and personal responsibility. If the potential is insufficient to satisfy these demands the state is disease".[17] This balance can differ between individuals and vary across different stages of life.[13] What Bircher describes as potential available for health, consisting of the sum of biologically given potential (e.g. genetic configuration) and personally acquired potential (e.g. education, developed abilities, healthy lifestyle), is also in line with Antonovsky's work.

At a conference for international health experts the preferred view on health was "the ability to adapt and to self-manage".[11] A description of three interacting domains of health was given. Firstly, physical health was described as the ability to maintain physiological homeostasis through changing circumstances. Secondly mental health consisted of the successful capacity to cope and recover from psychological stress, and incorporated Antonovsky's sense-of-coherence. Finally, social health included, among others, social participation.[11]

Reflecting on previous definitions and concepts, a comprehensive approach to conceptualizing health would include health and disease as a continuum, reflected as a dynamic balance between faced demands and an individual's capacity to adapt / self-manage. Furthermore, it would incorporate characteristics such as physical, mental, and social functioning, that can differ between persons and can change across different life stages, allowing for an individual to optimize his or her resources in order to feel healthy regardless of illness or disability. How specifically these concepts can be applied to different individuals, populations, and stages of life, such as menopause, remains to be elucidated.

Menopause: accident, disease, process or relief?

With advancing age, a woman's chance of achieving an ongoing pregnancy declines. This is predominantly dictated by a gradual decrease in both the quantity and the quality of oocytes, which reflects the process of ovarian ageing.[18] In the fourth month of the development of the female fetus the ovaries contain approximately 6-7 million oocytes, which is already reduced to a remaining 1–2 million primordial follicles at birth as a result of apoptosis.[19] The number of oocytes further decreases throughout life until finally the follicle pool is nearly depleted (count < 1000 follicles) and menopause is reached.[20] Menopause is defined by the World Health Organization (WHO) as the permanent cessation of menstruation due to the loss of ovarian follicular activity. The final menstrual period is retrospectively assigned after 12 consecutive months of amenorrhea, in absence of other pathological or physiological causes.[21] Menopause generally occurs around the age of 51 years, with a range between 40-60 years worldwide.[21 22] Studies in human natural fertility populations indicate that the end of natural fertility (i.e. sterility) occurs around the age of 41 years, with a similar variation in age as observed for age at menopause.[23 24] A similar variation is observed for the onset of menstrual cycle irregularities preceding menopause, which commonly occurs around the age of 46 years.[25] In 2001 the Stages of Reproductive Aging Workshop (STRAW) introduced specific terminology and staging criteria to define the various phases of reproductive ageing. Based on menstrual cycle pattern and qualitative follicle stimulating hormone (FSH) criteria the following phases were distinguished: 1. the (early, broad and late) reproductive stage, 2. the (early and late) menopausal transition, 3. the (early and late) postmenopause.[5] The biological processes encompassing menopause are part of a woman's life and should therefore not be regarded as a medical condition but as a natural phase of a woman's life cycle that extends beyond the ovaries and reproductive capacity, generating repercussions in all organs, tissues and all aspects of a woman's life. So what is healthy menopause exactly?

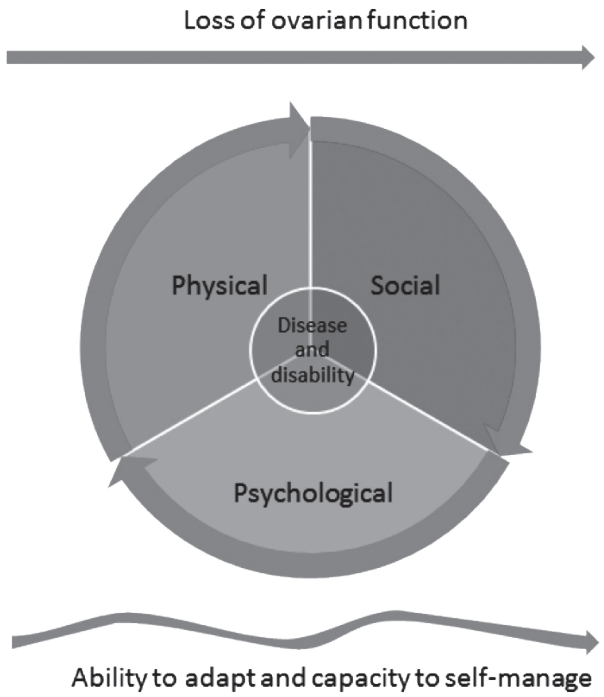
Healthy menopause: a conceptual framework

In order to summarize the existing body of literature regarding menopausal health, a search strategy with the elements "menopause" and "health" was performed in Embase.com (February 5th 2015). The search yielded 17.516 hits, of which the titles and abstracts of the top 500 articles after sorting by relevance ranking were screened. None of these articles attended to the overall concept of healthy menopause and a little over fifteen percent indirectly discussed key menopausal health subdomains such as sexual health or bone health. Overall, we were unable to identify any conceptual framework for healthy menopause.

In view of literature and the conceptual gaps, we propose to characterize healthy menopause by means of a user-based conceptual framework, positioning women and their needs at the center. This conceptualization can be seen as a further step in the maintenance, recovery, and improvement of health in middle-aged and elderly women from different perspectives, foremost the woman's own perspective, followed by the clinical, public health, and societal perspectives, and can be considered as a further step in delineating lines for future research.

We propose healthy menopause as (*Figure 1*):

Figure 1. Illustration of the proposed conceptual framework for healthy menopause. The terms physical, psychological, and social refer to self-perceived satisfactory physical, psychological, and social functioning.



A dynamic state, following the permanent loss of ovarian function, which is characterized by self-perceived satisfactory physical, psychological and social functioning, incorporating disease and disability, allowing the attainment of a woman's desired ability to adapt and capacity to self-manage.

The concept of healthy menopause applies to all women from the moment they enter the menopausal transition, up until they reach early and late postmenopause and includes women with spontaneous, iatrogenic, and premature menopause. Current evidence delineates the menopausal transition in particular as a period during which substantial short and long term alterations occur in different domains of women's health and quality of life.[5 8] Temporal health consequences include, among others, the manifestation of vasomotor symptoms, depression, and sleep disturbances.[26 27] Potential long term health risks include, among others, the development of osteoporosis, urogenital complaints, dyslipidemia, insulin resistance, and weight gain.[28-30] Furthermore, health-related quality of life (HRQoL) is a dimension of menopause as well as functioning, whereas overall quality of life (QoL) could be considered one of the dimensions of a woman's ability to adapt and capacity to self-manage, recognizing the importance of the distinction between HRQoL

as opposed to overall QoL.[31] Therefore, the transitional phase provides a unique window of opportunity to improve the future health status of women.

The conceptual framework emphasizes *self-perceived satisfactory* functioning and a woman's *desired* ability to adapt and her capacity to self-manage, hereby enabling her to determine and gain control over her health. It incorporates disease and disability, not necessarily implying that this will affect her sense of wellbeing and quality of life. Healthy menopause can be seen as a combination of obtained and developed resources utilized by a woman in order to maintain, revisit, adjust, recover, and improve the dynamic balance between every day opportunities and challenges. These resources expand at all levels and encompass women as a whole beyond their hormonal, reproductive, or physiological health.

Beyond the sum of all elements?

The cascade of hormonal changes through the menopausal transition can affect different body systems. In particular, changes in estradiol, FSH, and free androgen index coincide with an increase in cardiovascular risk, mood disorders, deteriorated mental and sexual functioning, and decreased bone density.[32] Within the concept of healthy menopause, different body systems could be considered subdomains of health related to physical, psychological, and social functioning.[8] It is beyond the scope of this paper to discuss each subdomain of health in detail. Nevertheless, a brief description of four major health subdomains is given below.

Cardiovascular risk. The incidence of cardiovascular disease (CVD), the leading single cause of death among women, increases substantially after menopause.[33-35] Adverse changes in cardiovascular risk factors during the menopausal transition may account for this increase in CVD risk. While proatherogenic changes in lipid profile seem to be specifically related to ovarian ageing, unfavourable changes in other cardiovascular risk factors may be more influenced by chronologic ageing.[36] Irrespective of the relative contributions of ovarian versus chronologic ageing to the increased CVD risk, the pre and perimenopausal period remains a critical time period in women's lifespan when increased attention to risk factor modification could reduce the risk for subsequent CVD events.

Mood and cognitive functioning. In general, women have a 2-fold greater risk for depression compared to men.[37] During the menopausal transition, an increased risk of depressed mood and experiencing a major depressive episode have been reported. Hormonal changes during menopause might partly account for the increased risk of depression.[38] While longitudinal studies of cognitive performance during the menopausal transition are scant, the impact of perimenopause on cognition appears to be subtle and transient.[39] Estrogen effects on serotonergic function may be a key mechanism relating mood and cognitive symptoms in the menopausal transition.[40]

Bone loss. While the results for the impact of menopausal transition on bone density are inconsistent, data from the Study of Women's Health across the Nation (SWAN) suggests that there is no to little change in bone mineral density at midlife in pre or early perimenopausal women. Bone loss increases substantially in the later perimenopause and remains rapid in the first few postmenopausal years.[41] In addition to estrogen deficiency, other risk factors such as low body weight and smoking also contribute to the pathogenesis of postmenopausal osteoporosis.[41]

Sexual functioning. The progressive decline of sex hormones together with psychosocial factors modulate vulnerability to sexual symptoms in menopause including low sexual desire, poor arousal and lubrication, dyspareunia, orgasmic dysfunction, and lack sexual pleasure.[42 43] The close link between sexual satisfaction and general physiological well-being of women makes sexuality an important element of healthcare for women at menopause.[44 45]

Beyond the aforementioned aspects, healthy menopause is characterized as an overarching concept at the intersection of multiple domains of health that could be measured in individuals and populations.

The numbers tell the tale?

A multidimensional concept asks for multidimensional measurements. Consequently there may be various approaches to measuring menopausal health. These approaches can be consolidated following the conceptual framework and could be subdivided into objective and subjective measures, of which a non-exhaustive overview can be found in *Table 1*. The choice of measurement instruments depends on the purpose of use, such as the evaluation of preventative or treatment interventions, research tools, and the needed perspective including the clinical, public health, societal, or individual perspective.

Objective measures only do not suffice in measuring healthy menopause for several reasons. Firstly, risk assessment is not the same as health assessment,[46] an example is the American Heart Association's concept of cardiovascular health that includes ideal health behaviour and health factor metrics.[47]

Secondly, although disease and disability are incorporated into the conceptual framework of healthy menopause, disease and disability will not necessarily affect an individual's sense of wellbeing and quality of life. This phenomenon is known as the disability paradox.[48-51] Health, disease, and disability can coexist at different degrees changing dynamically over time and across the life course. Thirdly, objective measures do not incorporate the woman-centered perspective of this framework for healthy menopause, i.e. self-perceived satisfactory functioning and desired ability to adapt and self-manage. Nevertheless, objective measures may influence, although not necessarily, how a woman perceives her own health. Therefore, a comprehensive approach for measuring menopausal health may be a combination of both objective and subjective measures.

Table 1. Non-exhaustive overview of measurement tools depicted per element of the overall concept of healthy menopause.

Element	Measurement tool examples	References
Menopause	WHO definition	21
	STRAW criteria	5
	Age-based	21 22
Functioning, disease and disability	36-item short-form	52
	EQ-5D	53
	Health-related (i.e. menopause related) QoL	54-62
	ADL / IADL	63 64
	COOP/WONCA charts	65
	Walking speed, grip strength	66-68
	Health domain specific diagnostic tools[a]	
	Productivity	69
	QALY/DALY	70-72
Ability to adapt and self-manage	None, thus partly via overall QoL[b]	73-75

[a] Examples of such diagnostic tools include, but are not limited to, the guideline on the assessment of cardiovascular risk,[76] the 6-minute walking test,[77] or the CESD/HADS depression and/or anxiety scales.[78 79]
[b] We are not aware of any available instrument to measure objective and subjective ability to adapt and self-manage. Nevertheless, overall quality of life might be valid as one of the dimensions of the ability to adapt and to self-manage.
ADL=activities of daily living, CESD=Center for Epidemiologic Studies Depression Scale, COOP/WONCA=Dartmouth Primary Care Cooperative Information Project/World Organization of Family Doctors, DALY=disability-adjusted life year, EQ-5D=EuroQol-5D, HADS=hospital anxiety and depression scale, IADL=instrumental activities of daily living, QALY=quality-adjusted life year, QoL=quality of life, SEIQoL=schedule for the evaluation of individual quality of life, STRAW=Stages of Reproductive Aging Workshop, WHO=World Health Organization.

Such a battery of comprehensive measurement methods could provide valuable information about aspects of menopausal health. However, the vast majority of these measurements fail to account for the multidimensional concept of healthy menopause as a whole and would need to be complemented by additional tools. The conceptualization of healthy menopause could be an initial step in designing tools to assess this multidimensional concept.

Putting things to practice

This unifying conceptual framework could facilitate the improvement of adequate preventative and treatment strategies, guide scientific efforts, and aid education and communication to health care practitioners and the general public. The menopausal

transition is an opportune time for general education, recognition of signs and symptoms, promotion of healthy lifestyle, individualized counseling, and evaluation and possible treatment of modifiable risk factors. Recognizing this overarching, gradual, and comprehensive impact that the menopausal transition has in women, could aid women, professionals, and policy makers in their approach towards the realization of healthy menopause.

Experiences from other fields that have made important transitions from a disease reduction to a health promotion perspective, such as sexual and cardiovascular health, could well serve as an example for successful implementation of the concept of healthy menopause.[43 47] Taking into account the user-based framework, a coordinated bottom-up approach is warranted. To significantly improve healthy menopause, professionals and policy makers should enhance women's abilities to optimally cope with menopausal changes at midlife, and first embrace the overarching concept of healthy menopause and consider women as individuals rather than specific organs or domains. This approach could further contribute to improve women's conditions and health, allowing the achievement of their potential and the fulfillment of their fundamental role in society.

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Author contributions

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Disclosures

With regard to potential conflicts of interest, there is nothing to disclose.

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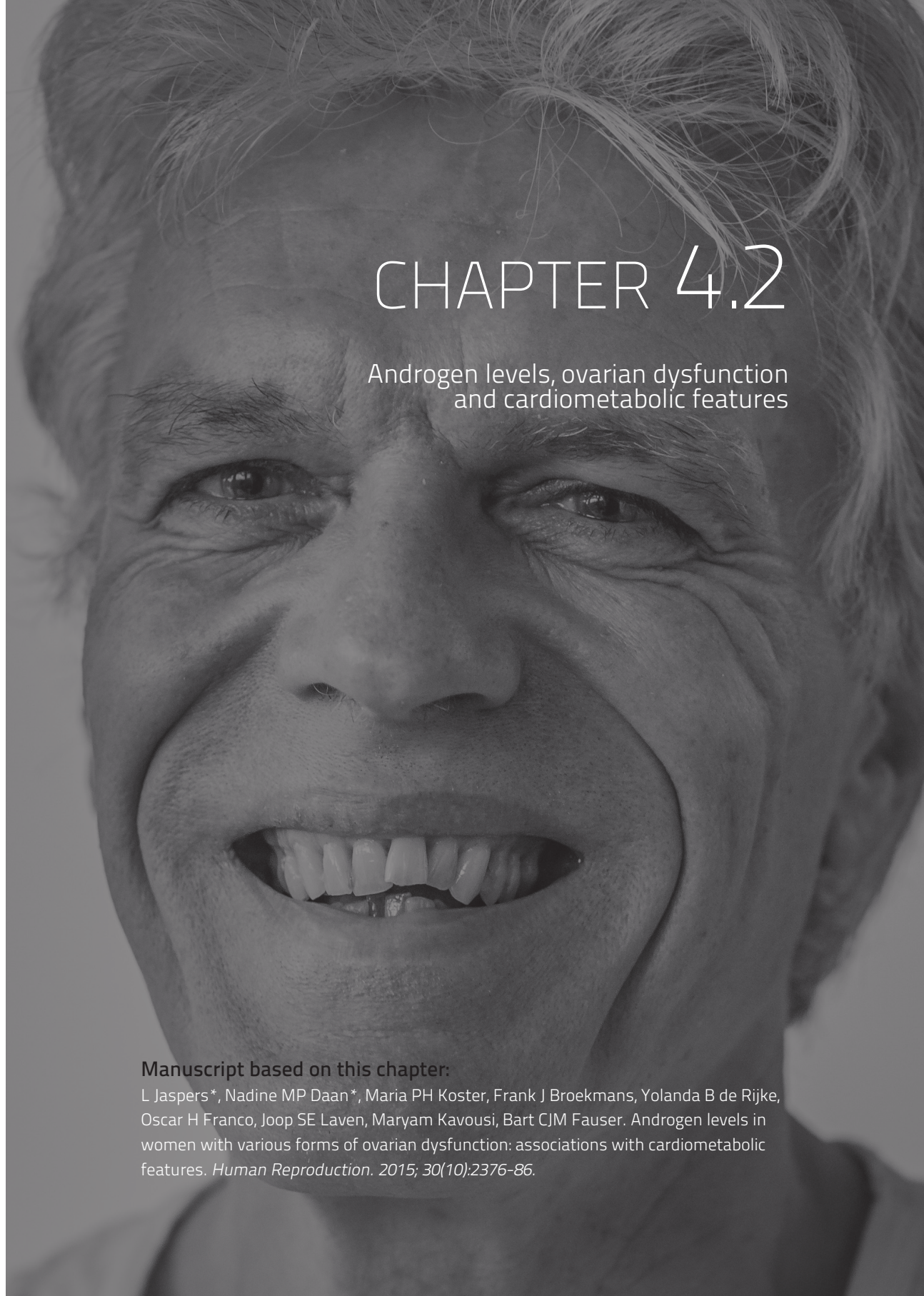


CHAPTER 4.2

Androgen levels, ovarian dysfunction and cardiometabolic features

Manuscript based on this chapter:

L Jaspers*, Nadine MP Daan*, Maria PH Koster, Frank J Broekmans, Yolanda B de Rijke, Oscar H Franco, Joop SE Laven, Maryam Kavousi, Bart CJM Fauser. Androgen levels in women with various forms of ovarian dysfunction: associations with cardiometabolic features. *Human Reproduction. 2015; 30(10):2376-86.*

ABSTRACT

Background:
Sex steroid hormones play important roles in the development of cardiovascular diseases (CVD). Extremes in low as well as high androgen levels have been associated with increased CVD risk in both men and women.

Objectives:
To assess whether differences in androgen levels in women with various forms of ovarian dysfunction are associated with cardiometabolic abnormalities.

Design, setting, and participants:
Cross-sectional study in 680 women with polycystic ovary syndrome (PCOS), premature ovarian insufficiency (POI), natural postmenopausal women (NM), or regular menstrual cycles (RC) (170 women per group).

Main measures:
Measurements of serum testosterone, androstenedione and dehydroepiandrosterone sulfate using liquid chromatography-tandem mass spectrometry. Assessments were taken of body mass index (BMI), blood pressure, lipid profiles, glucose, insulin, and SHBG, and the bioactive fraction of circulating testosterone was calculated using the free androgen index (FAI).

Results:
PCOS women were hyperandrogenic (median FAI = 4.9 (IQR 3.6 to 7.4)), and POI women were hypoandrogenic (FAI = 1.2 (0.8 to 1.7)) compared with RC women (FAI = 1.7 (1.1 to 2.8)) after adjustment for age, ethnicity, smoking, and BMI ($p<0.001$). After adjustment for age, there were no significant differences in androgens between POI and NM ($p=0.15$) and between NM and RC ($p=0.27$) women, the latter indicating that chronological ageing rather than ovarian ageing influences the differences between pre-and postmenopausal women. A high FAI was associated with elevated triglycerides (ß log FAI for PCOS: 0.45, $p<0.001$, POI: 0.25, $p<0.001$, NM: 0.20, $p=0.002$), insulin (ß log FAI for PCOS: 0.77, POI: 0.44, NM: 0.40, all $p<0.001$), HOMA-IR (ß log FAI for PCOS: 0.82, POI: 0.46, NM: 0.47, all $p<0.001$), and mean arterial pressure (ß log FAI for PCOS: 0.05, $p=0.002$, POI: 0.07, $p<0.001$, NM: 0.04, $p=0.04$) in all women, with increased glucose (ß log FAI for PCOS: 0.05, $p=0.003$, NM: 0.07, $p<0.001$) and decreased high-density lipoprotein (ß log FAI for PCOS: -0.23, $P < 0.001$, NM: -0.09, $p=0.03$) in PCOS and NM, and with increased low-density lipoprotein (ß log FAI for POI: 0.083, $p=0.041$) in POI women. Adjustment for BMI attenuated the observed associations. Associations between FAI and cardiometabolic features were the strongest in PCOS women, even after adjustment for BMI

Conclusions:
Androgen levels differed substantially between women with and without ovarian dysfunction, and increased androgen levels were associated with impaired cardiometabolic features in all women irrespective of their clinical condition. This study affirms the potent effect of androgens on cardiometabolic features, indicating that androgens should indeed be regarded as important denominators of women's health. Future research regarding the role of androgens in the development of CVD and potential modulatory effects of BMI is required.

Keywords: PCOS, POI, menopause, androgens, cardiovascular risk factors

INTRODUCTION

Sex steroid hormones are recognized to play a crucial role in the development of cardiovascular disease (CVD) in men and women.[1] Although CVD is more prevalent amongst men, the incidence of CVD in women increases steadily beyond 50 years of age.[2] Consequently, CVD currently represents the world's leading cause of death in women.[3] This rise in CVD incidence in women has been previously attributed to a decline in premenopausal estrogen levels following the menopausal transition.[4] More recently, research has extended our understanding of the potential role of androgens in the development of CVD both in men and women.

Various studies in both sexes have proposed that extremes of low as well as high androgen concentrations are associated with increased CVD risk.[5-7] In men, low androgens have been associated with dyslipidemia, increased body mass index (BMI), diabetes, hypertension and CVD mortality.[8 9] Several studies in postmenopausal women have also reported an inverse relation between endogenous androgen levels, dyslipidemia and atherosclerosis.[10-12] Furthermore, improvements in lipid profiles following estradiol/testosterone replacement therapy have been reported in postmenopausal women.[13 14]

In contrast, increased androgen concentrations have been shown to impair cardiovascular health in both men and women.[15 16] Women with polycystic ovary syndrome (PCOS), especially those with hyperandrogenism, exhibit an increased prevalence of dyslipidemia, insulin resistance, obesity and CVD.[17 18] Moreover, supplementation of androgens in postmenopausal women has been associated with decreased insulin sensitivity and with dyslipidemia.[19] A chronically induced hyperandrogenic state appears to cause atherogenicity through inflammation, as demonstrated in female to male transsexuals treated with testosterone.[20]

In women, androgens are produced in the ovaries, in the adrenal cortex and through peripheral conversion of precursor hormones.[21] Decreased levels of circulating androgens have been reported in women with premature ovarian insufficiency (POI), who experience menopause before the age of 40 years.[22 23] POI has been identified as a risk factor for the development of CVD.[24]

In this study, we aimed to compare androgen levels measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS) and assess their associations with cardiometabolic features in women under different clinical conditions: PCOS (associated with hyperandrogenism), POI (associated with hypoandrogenism), women who experienced natural menopause (NM) and women of reproductive age with regular menstrual cycles (RC).

METHODS

Study population

Four groups of women were included in this study: women previously diagnosed with PCOS, women previously diagnosed with POI, women who experienced natural menopause (NM) and women of reproductive age with regular menstrual cycles (RC).

The included women with PCOS or POI participated in a large prospective cohort study on menstrual cycle disturbances within the reproductive outpatient clinic of the University Medical Center Utrecht between November 2004 and July 2011. Women were screened according to a standardized protocol consisting of medical/reproductive history, anthropometric measurements, transvaginal ultrasonography and an extensive fasting endocrine/metabolic laboratory evaluation. Spare serum samples were collected and stored at -20 degrees Celsius. The screening procedure has been previously described in detail elsewhere.[25 26] This study was conducted with approval of the local institutional ethical review board, and all participants provided written informed consent. The study was registered on www.clinicaltrials.gov with trial number NCT0230904.

PCOS was diagnosed according to the Rotterdam criteria, if at least two of the following characteristics were present: ovulatory dysfunction, androgen excess and/or polycystic ovarian morphology.[27] Ovulatory dysfunction was defined as an average menstrual cycle length of 35 days to six months (oligomenorrhea) or absence of a menstrual bleeding for ≥ 6 months (amenorrhea). For the current study, we selected women with an anticipated hyperandrogenic PCOS phenotype, based on the primary clinical and biochemical assessment of hyperandrogenism. Clinical and biochemical hyperandrogenism were defined as a Ferriman-Gallwey score>8, and/or a free androgen index (FAI)>4.5 (FAI: (Testosterone / SHBG) x 100)).[28] POI was defined as secondary amenorrhea ≥ 4 months occurring before the age of 40 years with accompanying FSH levels above 40 IU/L.[29] Women with POI were excluded if they had a history of past ovarian surgery and/or gonadotoxic treatment such as chemotherapy or radiation therapy.

Included NM women were selected from the Rotterdam Study. The Rotterdam Study is a large prospective population-based cohort study of men and women of 45 years of age and older, which was initiated in 1990 in Ommoord, a suburb of Rotterdam, the Netherlands. This study has been designed to investigate the incidence and risk factors for various chronic illnesses such as cardiovascular and endocrine diseases, as has been previously described in detail.[30] For the current study, women who experienced natural menopause after the age of 45 years, with a history of previous regular menstrual cycles throughout their reproductive life were selected.

Included RC women were participants in a preconceptional cohort study in women starting IVF/ICSI treatment within the reproductive outpatient clinic of the University

Medical Center Utrecht between October 2006 and November 2013. This study was registered on www.clinicaltrials.gov with trial number NCT02309073. For the current study we included women undergoing IVF/ICSI treatment with the indication of severe male infertility, since these women were clinically evaluated and exhibited no signs of female reproductive dysfunction. Severe male infertility was defined as a semen analysis with volume × concentration × motility of < 2.0 million. Included women reported a regular mean menstrual cycle length between 21-35 days.
None of the women included in this study were using any form of hormonal therapy/contraception for at least six weeks prior to the moment of blood withdrawal. The current study was conducted with institutional ethical review board permission and all included women provided written informed consent.

Endocrine and metabolic assessment

In all women testosterone, dehydroepiandrosterone sulfate (DHEAS), and androstenedione were measured with LC-MS/MS in serum samples that were previously stored at -20 degrees Celsius.
All steroid hormones were measured simultaneously with a LC-MS/MS method using the CHS™ MSMS Steroids Kit (Perkin Elmer, Turku, Finland).The Steroids Kit uses a combined solvent extraction and protein precipitation method with acetonitrile containing the deuterated internal standards 2H5-androstenedione, $^{2}H_{8}$-17 α-hydroxyprogesterone and $^{2}H_{5}$-testosterone. The internal standards undergo processing identical to the analytes. The chromatographic separation was performed on a Waters® Acquity™ UPLC HSS T3 1.8 µm column (diameter 1 mm, length10 cm) and in-line filter frit 0.2 µm with acetonitrile/MeOH gradient. A Waters XEVO-TQ-S system (Waters, Milford, MA, USA) equipped with an ESI source operating in the electrospray positive mode except for DHEAS (negative ESI). Multiple reaction monitoring was applied for the detection of the analytes using both quantifiers and qualifiers. The corresponding inter-assay coefficients of variation and lower limit of quantification (LLOQ) are the following: androstenedione <6.5%; LLOQ 0.20 nmol/L, DHEAS <5.9%; LLOQ 0.25 µmol/L, and testosterone <5%; LLOQ 0.07 nmol/L.

In women with PCOS or POI, serum was drawn at the outpatient clinic in which insulin, glucose, SHBG and lipids were directly assessed. Insulin and SHBG were assessed with the Immulite 1000 assay (Diagnostics Products Corporation Breda, Netherlands) until April 2007 and thereafter with the Roche Modular E170 (Roche Diagnostics, Almere, Netherlands). (Conversion formula: Roche Modular E170 = 1.10 x (Immulite 1000) - 0.7). Glucose and lipids were assessed with the VITROS Chemistry System (Ortho-Clinical Diagnostics, Strasbourg, France) until November 2006 and then with the Unicell DxC 800 assay (Beckman Coulter, Woerden, Netherlands).
The corresponding intra- and interassay coefficient of variation with lower limit of detection (LLOD) of the last used assays were insulin <2 and <4%; LLOD: 0.5 mE/L, SHBG <2 and <5%; LLOD: 0.35 nmol/L, glucose <4 and <4%; LLOD: 0.3 mmol/L, lipids <2 and <3%; LLOD: 0.1 mmol/L.

In natural postmenopausal women, serum was drawn during their evaluation for the Rotterdam Study, and insulin, glucose, SHBG and lipid profiles were directly assessed. Insulin and SHBG were determined using Immulite 2000Xpi (Diagnostics Products Corporation Breda). Glucose and lipids were assessed using the COBAS 8000 system (Roche Diagnostics). The corresponding intra- and interassay coefficients of variation with the LLOD of the last used assays were insulin <6 and <8%; LLOD: 14 pmol/L, SHBG <4 and < 5%; LLOD: 0.02 nmol/L, glucose <0.8 and < 1.4%; LLOD: 0.11 mmol/L, lipids <1.1 and <2.1%; LLOD: 0.1 mmol/L.

There were no metabolic parameters available of the women of reproductive age with regular menstrual cycles. In these women, SHBG was assessed in serum samples that were previously stored at -20 degrees Celsius.

Hormones included in the statistical analyses were testosterone, DHEAS, androstenedione, SHBG and the calculated FAI. Cardiometabolic features included in the analyses were total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides (TG), insulin and glucose. The calculated homeostasis model assessment-insulin resistance (HOMA-IR; (glucose x insulin)/22.5) and mean arterial pressure (MAP; (2 x diastolic+systolic)/3)) were additionally included.[31 32]

Statistical analyses

A power calculation was performed based on the groups in which we expected to detect the smallest difference in the concentration of total testosterone (i.e. women with POI). We expected a clinically significant lower testosterone level in the POI group of 1.12 nmol/L (SD ± 0.58) versus a testosterone of 1.36 nmol/L in women with regular menstrual cycles (RC).[22] To obtain a power of 0.9 with a significance level of 0.05/4=0.0125 (applying Bonferroni correction for multiple testing), 167 patients needed to be included in the current study. Taking into account potential processing/measuring errors, a total of 170 patients were included in each group.

The primary research aim was to assess androgen levels and cardiometabolic characteristics in PCOS, POI, NM and RC women. All hormone levels and cardiometabolic features were log-transformed to obtain normally distributed variables. Crude and adjusted means were calculated and stratified per group using linear regression analyses. Due to the large age difference between the four groups, model 1 was primarily adjusted for age. Model 2 was adjusted for age, ethnicity and smoking, and could be considered the fully adjusted model. Since BMI is most likely an intermediate in the causal pathway between androgens and cardiometabolic characteristics, for instance, through direct inhibition of SHBG production and stimulation of insulin-like growth factor (IGF-I) production, adjusting for BMI could potentially result in an overadjustment.[33] Nevertheless, a third model including BMI was made. Furthermore, androgen levels and cardiometabolic features between the four groups of women were compared. Due to

large differences between the four groups of women, age differences in particular, we were not able to assign one reference group as this would result in unequal comparisons. Subsequently, we chose to make 4 specific one to one comparisons in order to obtain the most illustrative results. For androgen levels these comparisons were: PCOS versus RC, POI versus RC, POI versus NM and NM versus RC. In the absence of values for the RC group, we compared cardiometabolic features between the following groups: PCOS versus POI and POI versus NM. T-tests were used to assess crude statistical differences and linear regression with a dichotomous class variable (e.g. PCOS 1 vs. RC 0) for (multi) variable adjusted statistical differences.

The secondary research aim was to assess potential associations between androgen levels and the cardiometabolic features for women with PCOS, POI or NM. The FAI was used as a proxy for the androgen concentrations since it reflects the bioactive proportion of circulating testosterone levels. Associations were first depicted in scatterplots and subsequently assessed using linear regression analyses. Cardiometabolic features were used as the dependent and the FAI as independent variable, and adjusted for the same covariates as in models 1-3 of the primary research aim. Furthermore, we assessed whether the association between FAI and cardiometabolic features was significantly different for POI versus NM and PCOS versus POI women (p-value for interaction).

SPSS version 21.0 was used for all analyses. Associations were considered statistically significant at a p-value of <0.05 after applying a Bonferroni correction for the number of performed comparisons.

RESULTS

The baseline characteristics, median androgen concentrations and cardiometabolic characteristics of participating women with PCOS, POI, NM and RC are outlined in *Table 1*. Women were predominantly from Northern European descent. The majority of women in the PCOS and NM group were overweight (64 and 62%, respectively). *Figure 1* shows the multivariable adjusted mean FAI of each group, which was used as a proxy for the androgen concentrations in further analyses. After adjustment for age, ethnicity, smoking and BMI, the FAI remained highest in women with PCOS, followed by the RC, NM, and POI women (*Figure 1*).

The differences in androgen concentrations between the four study groups are shown in *Table 2*. Women with PCOS exhibited a 3-fold increase in absolute FAI and a 2-fold increase in absolute testosterone levels compared with RC women, which remained significant after correction for age, ethnicity, smoking and BMI (both p<0.001). Women with POI exhibited a 30% decrease in absolute FAI and 12% decrease in absolute testosterone levels compared with RC women, which remained significant after correction for age,

Table 1. Characterictics of the study population.

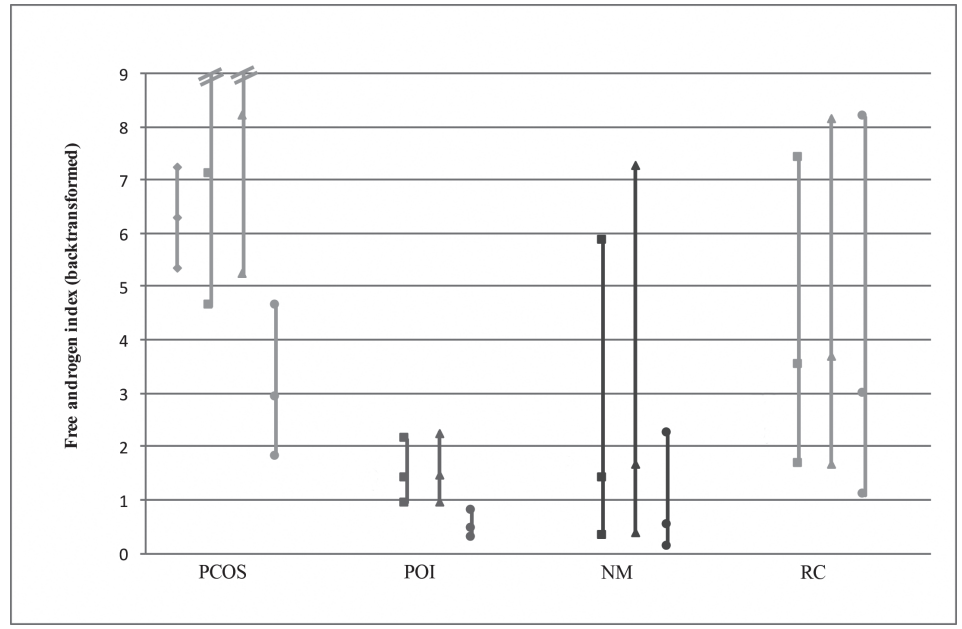
General characteristics	PCOS (n=170)	POI (n=170)	NM (n=170)	RC (n=170)
Age (years)	27.0 (23.0 to 31.0)	37.0 (34.0 to 40.0)	55.8 (53.2 to 58.3)	33.0 (29.0 to 36.0)
Age at menopause (years)	NA	35.0 (29.3 to 37.0)	52.0 (50.0 to 54.0)	NA
Time since menopause (years)	NA	1.0 (0.0 to 3.0)	3.5 (2.3 to 4.9)	NA
Northern European descent (yes)	122 (72%)	134 (79%)	157 (92%)	145 (85%)
Current smoking (yes)	37 (22%)	45 (27%)	40 (24%)	24 (14%)
BMI (kg/m^2)	27.7 (23.4 to 32.5)	23.0 (21.4 to 26.6)	26.3 (24.0 to 29.1)	23.4 (21.7 to 25.9)
Overweight (BMI ≥ 25)	108 (64%)	62 (37%)	106 (62%)	52 (31%)
Waist circumference (cm)	91.0 (78.0 to 104.0)	80.0 (75.0 to 90.0)	85.4 (80.3 to 93.6)	NA
Systolic blood pressure (mmHG)	122.0 (116.0 to 133.0)	122.0 (113.0 to 135.0)	127.0 (116.0 to 140.0)	NA
Diastolic blood pressure (mmHG)	79.0 (73.0 to 85.0)	80.0 (73.0 to 88.0)	81.0 (75.0 to 89.3)	NA
MAP (mmHG)	93.3 (87.7 to 101.0)	95.0 (86.2 to 102.2)	97.3 (89.3 to 106.8)	NA
Hypertension (≥140 systolic and/or 90 diastolic mmHg)	36 (21%)	44 (26%)	67 (39%)	NA
Testosterone (nmol/L)	1.6 (1.3 to 2.01)	0.7 (0.5 to 0.9)	0.8 (0.6 to 1.0)	0.8 (0.6 to 1.0)
Androstenedione (nmol/L)	7.6 (6.3 to 9.5)	2.4 (1.9 to 3.2)	2.4 (1.9 to 3.4)	3.5 (2.7 to 4.5)
DHEAS (µmol/L)	5.2 (3.7 to 6.7)	3.5 (2.6 to 4.8)	2.5 (1.6 to 3.5)	4.0 (2.9 to 5.8)
SHBG (nmol/L)	32.0 (22.9 to 44.0)	54.0 (38.9 to 75.8)	56.3 (41.2 to 77.7)	48.5 (33.8 to 62.2)
FAI	4.9 (3.6 to 7.4)	1.2 (0.8 to 1.7)	1.3 (1.0 to 2.0)	1.7 (1.1 to 2.8)
Total cholesterol (mmol/L)	4.6 (4.1 to 5.2)	5.0 (4.5 to 5.7)	5.8 (5.2 to 6.4)	NA
HDL cholesterol (mmol/L)	1.2 (1.0 to 1.6)	1.7 (1.4 to 1.9)	1.6 (1.3 to 1.9)	NA

Table 1. Continued

General characteristics	PCOS (n=170)	POI (n=170)	NM (n=170)	RC (n=170)
LDL cholesterol (mmol/L)	2.8 (2.4 to 3.3)	3.0 (2.5 to 3.4)	3.6 (3.1 to 4.2)	NA
Triglycerides (mmol/L)	0.8 (0.5 to 1.2)	0.8 (0.5 to 1.0)	1.1 (0.8 to 1.5)	NA
Glucose (mmol/L)	5.1 (4.9 to 5.4)	5.1 (4.8 to 5.4)	5.1 (4.9 to 5.4)	NA
Insulin (mIU/L)	10.4 (6.5 to 18.1)	6.5 (3.9 to 10.4)	8.4 (6.5 to 13.4)	NA
HOMA-IR	2.3 (1.5 to 4.1)	1.6 (0.8 to 2.3)	2.0 (1.4 3.1)	NA

Continuous parameters are presented as medians with interquartile ranges, categorical variables as absolute numbers with percentages.
BMI=body mass index, DHEAS=dehydroepiandrosterone sulfate, FAI=free androgen index, HOMA-IR=homeostasis model assessment-insulin resistance, MAP=mean arterial pressure, NA=not applicable, NM=natural menopausal women, PCOS=polycystic ovary syndrome, POI=premature ovarian insufficiency, RC=women with regular menstrual cycles, SHBG=sex hormone–binding globulin.

Figure 1. Adjusted backtransformed means and confidence interval of the free androgen index.



Square, model 1 is adjusted for age. Triangle, model 2 is adjusted for age, ethnicity, and smoking. Circle, model 3 is adjusted for age, ethnicity, smoking, and BMI. The upper bounds of the confidence interval of models 1 and 2 in the PCOS group have been truncated (10.87 and 12.83, respectively). NM=women who experienced natural menopause, PCOS=polycystic ovary syndrome, POI=premature ovarian insufficiency, RC=women with regular menstrual cycles.

ethnicity, smoking and BMI (p<0.001 and p=0.002, respectively). After adjustment for age, there were no significant differences in FAI, SHBG and androgen concentrations between POI versus NM and NM versus RC. Additional adjustment for other covariates did not alter these findings.

The differences in cardiometabolic features between PCOS versus POI and POI versus NM women are outlined in *Table 3*. After correcting for age, ethnicity and smoking, we found significant differences in HDL cholesterol (p<0.001), TG (p=0.001), insulin (p<0.001) and HOMA-IR (p<0.001) between (hyperandrogenic) PCOS and (hypoandrogenic) POI women. After additional adjustment for BMI, only HDL cholesterol levels remained significantly decreased in PCOS compared to POI women (1.2 versus 1.7 mmol/L, respectively; p<0.001). When comparing POI and NM women, significant differences were found for MAP and insulin levels in models adjusted for age, ethnicity and smoking (p<0.001 and p=0.013, respectively). After additional adjustment for BMI, only MAP remained significantly different between POI and NM women (Table 3).

Table 2. P-values for differences in androgens, SHBG and FAI between groups.

		PCOS vs. RC	POI vs. RC	POI vs. NM	RC vs. NM
Testosterone	Model 1	**<0.001**	**0.002**	0.15	0.27
	Model 2	**<0.001**	**0.001**	0.24	0.35
	Model 3	**<0.001**	**0.002**	0.31	0.47
Androstenedione	Model 1	**<0.001**	**<0.001**	0.14	0.49
	Model 2	**<0.001**	**<0.001**	0.17	0.20
	Model 3	**<0.001**	**<0.001**	0.15	0.19
DHEAS	Model 1	0.43	0.12	0.96	0.73
	Model 2	0.49	0.06	0.91	0.51
	Model 3	0.37	0.07	0.85	0.43
SHBG	Model 1	**<0.001**	**<0.001**	0.60	0.35
	Model 2	**<0.001**	**<0.001**	0.55	0.31
	Model 3	0.16	**<0.001**	0.83	0.18
FAI	Model 1	**<0.001**	**<0.001**	0.12	0.99
	Model 2	**<0.001**	**<0.001**	0.17	0.85
	Model 3	**<0.001**	**<0.001**	0.51	0.56

Model 1 is adjusted for age.
Model 2 is adjusted for age, ethnicity and smoking.
Model 3 is adjusted for age, ethnicity, smoking and BMI (conservative model).
P-values in bold are significant at p=0.05 after Bonferroni correction for 4 comparisons (i.e. p<0.0125).
DHEAS=dehydroepiandrosterone sulfate, FAI=free androgen index, NM=natural menopausal women, PCOS=polycystic ovary syndrome, POI=premature ovarian insufficiency, RC=women with regular menstrual cycles, SHBG=sex hormone-binding globulin.

The multivariable adjusted associations between FAI and cardiometabolic features, stratified for PCOS, POI, and NM women, are depicted in *Supplemental Figure 1-3.* Details regarding exact effect sizes and p-values can be found in *Supplemental Table 1*.

The associations between FAI and cardiometabolic features in age-adjusted models (*Supplemental Figure I*) did not substantially change after additional adjustment for ethnicity and smoking (*Figure 2*). After adjustment for age, ethnicity and smoking, a high FAI was significantly associated with higher TG (ß for PCOS: 0.45, POI: 0.25, NM: 0.20), insulin (ß for PCOS: 0.77, POI: 0.44, NM: 0.40), HOMA-IR (ß for PCOS: 0.82, POI: 0.46, NM: 0.47), and MAP in all women (ß for PCOS: 0.05, POI: 0.07, NM: 0.04), and with high glucose levels in PCOS and NM women only (ß for PCOS: 0.05, NM: 0.07). A high FAI was associated with lower HDL cholesterol in PCOS and NM women (ß for PCOS: -0.23, NM: -0.09), and with higher LDL cholesterol in POI women (ß: 0.08). No significant associations were found for total cholesterol in either of the study groups. All exact effect sizes (ß's) are

Table 3. P-values for differences in cardiometabolic parameters between groups.

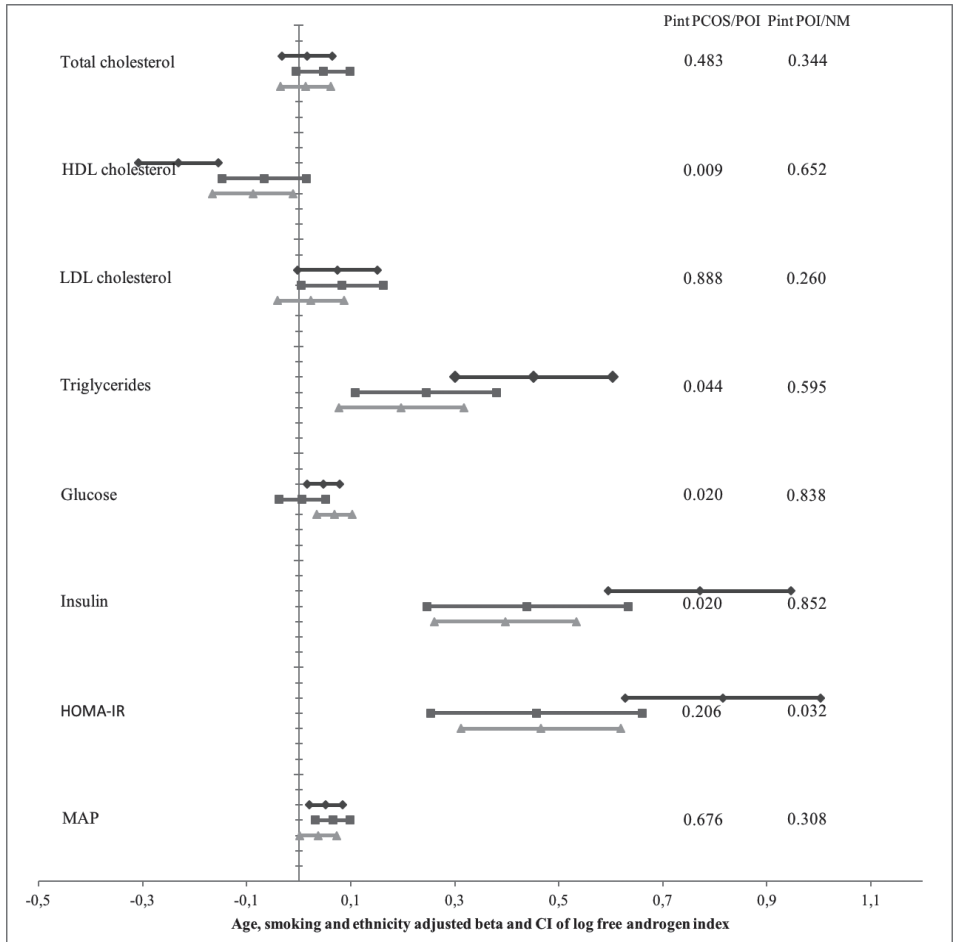
		PCOS vs. POI	POI vs. NM
Mean arterial pressure	Model 1	0.03	**0.004**
	Model 2	0.06	**<0.001**
	Model 3	0.56	**0.009**
Total cholesterol	Model 1	0.28	0.84
	Model 2	0.28	0.78
	Model 3	0.26	0.90
HDL cholesterol	Model 1	**<0.001**	0.03
	Model 2	**<0.001**	0.06
	Model 3	**<0.001**	0.19
LDL cholesterol	Model 1	0.29	0.21
	Model 2	0.29	0.24
	Model 3	0.97	0.38
Triglycerides	Model 1	**0.001**	0.37
	Model 2	**0.001**	0.37
	Model 3	0.53	0.87
Glucose	Model 1	0.53	0.86
	Model 2	0.63	0.94
	Model 3	0.44	0.69
Insulin	Model 1	**<0.001**	**0.016**
	Model 2	**<0.001**	**0.013**
	Model 3	0.04	0.06
HOMA-IR	Model 1	**<0.001**	0.03
	Model 2	**<0.001**	0.02
	Model 3	0.07	0.10

Model 1 is adjusted for age.
Model 2 is adjusted for age, ethnicity and smoking.
Model 3 is adjusted for age, ethnicity, smoking and BMI (conservative model). P-values in bold are significant at p=0.05 after Bonferroni correction for 3 comparisons (i.e. p<0.0167).
HOMA-IR=homeostasis model assessment insulin resistance, NM=natural menopausal women, PCOS=polycystic ovary syndrome, POI=premature ovarian insufficiency, RC=women with regular menstrual cycles.

depicted in Supplemental Table I.

When comparing the associations between androgens and cardiometabolic features in PCOS versus POI women, there were significant differences in P-values for interaction regarding HDL cholesterol (p=0.009), HOMA-IR (p=0.020) and insulin (p=0.020), indicative of a stronger association between FAI and cardiometabolic features in PCOS women than POI women. The p-values for interaction were non-significant for all cardiometabolic

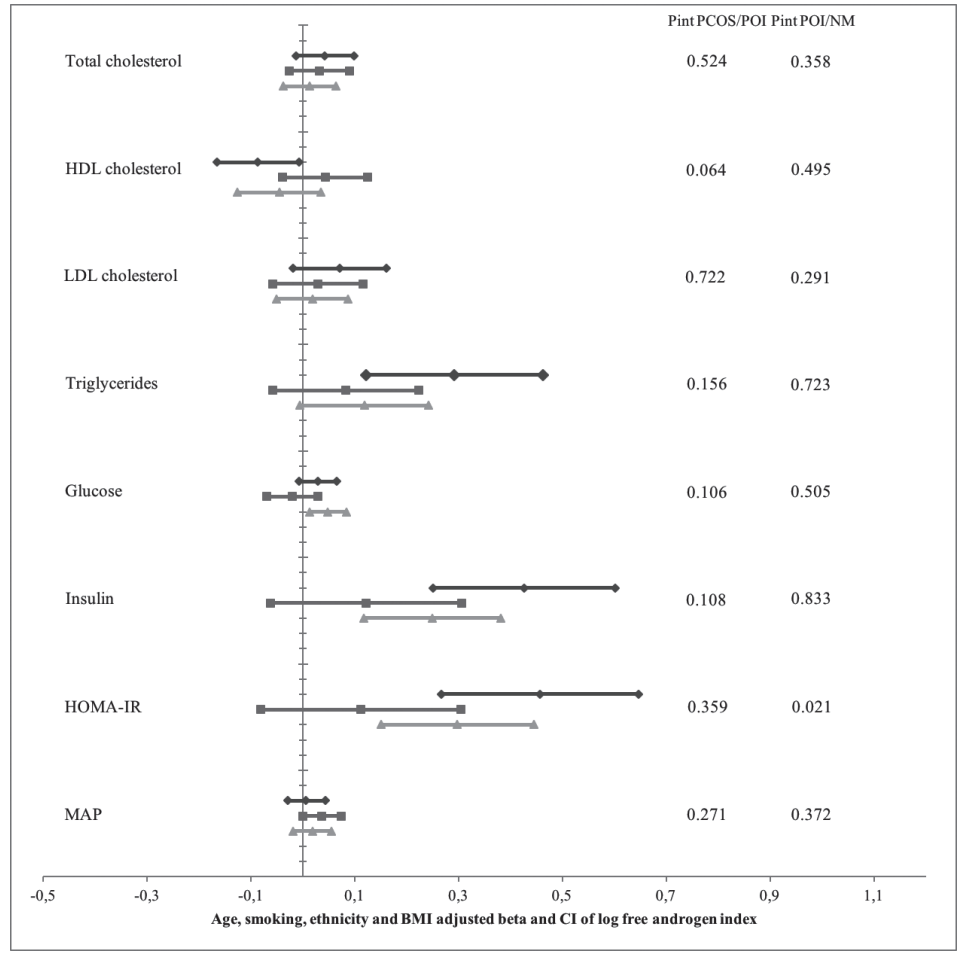
Figure 2. Associations between log free androgen index and cardiometabolic parameters for NM, POI and PCOS women, adjusted for age, smoking, and ethnicity.



Positive associations are depicted on the right side of the null line; negative associations are depicted on the left side of the null line. Associations are significant when the confidence interval (visualized as the horizontal line) does not reach the vertical null line.
HOMA-IR=homeostasis model assessment-insulin resistance, NM=natural menopausal women, MAP=mean arterial pressure, PCOS=polycystic ovary syndrome, P-int=p-value for interaction, POI=premature ovarian insufficiency.

features when comparing POI versus NM, indicating that the associations between FAI and cardiometabolic features do not differ between these women.
When models were additionally adjusted for BMI (*Figure 3*), the FAI remained associated with HDL cholesterol (ß: -0.09), TG (ß: 0.29), insulin (ß: 0.43) and HOMA-IR (ß: 0.46) only in women with PCOS. After adjustment for BMI, there were no significant associations

Figure 3. Associations between log free androgen index and cardiometabolic parameters for NM, POI and PCOS women, adjusted for age, smoking, ethnicity, and BMI.



Positive associations are depicted on the right side of the null line; negative associations are depicted on the left side of the null line. Associations are significant when the confidence interval (visualized as the horizontal line) does not reach the vertical null line.
HOMA-IR=homeostasis model assessment-insulin resistance, NM=natural menopausal women, MAP=mean arterial pressure, PCOS=polycystic ovary syndrome, P-int=p-value for interaction, POI=premature ovarian insufficiency.

between FAI and cardiometabolic features in POI women. In NM women, only glucose (ß: 0.05), insulin (ß: 0.25), and HOMA-IR (ß: 0.30) remained significantly associated with FAI after adjustment for BMI.

DISCUSSION

The primary aim of the current study was to compare androgen levels assessed by LC-MS/MS and to explore its potential association with various cardiometabolic features in women under different clinical conditions (i.e. PCOS, POI, NM and RC). As expected, we found women with PCOS to be hyperandrogenic, and women with POI to be hypoandrogenic, compared to RC women. Differences in androgens between NM versus POI and NM versus RC, were no longer significant after adjusting for age.

The second research aim of this study was to assess potential associations between androgen levels and cardiometabolic features in these women. We found that a higher FAI was associated with increased cardiovascular risk factors, i.e. elevated TG, insulin, HOMA-IR, and MAP in all women. A high FAI was also associated with increased glucose and decreased HDL levels in women with PCOS and NM, and with increased LDL in POI women. Adjustment for BMI substantially attenuated these associations. The strongest associations were observed in women with PCOS, even after adjustment for BMI.

In women, numerous studies have been performed concerning changes in androgen concentrations with age and following the menopausal transition. Previous cross-sectional studies have described lower androgen levels in postmenopausal women compared to premenopausal women, suggesting an association between androgen concentrations and menopausal status.[34 35] However, most longitudinal studies demonstrated a continuous decline in total testosterone, DHEAS and androstenedione levels with age, with no or very little variation occurring in relation to the menopausal status.[21 36 37] Our finding that androgen levels between POI vs. NM and NM vs. RC did not differ significantly after adjustment for age, further supports the results from these longitudinal studies.

In the current study we observed that an increase in FAI is associated with various cardiometabolic derangements in all women, irrespective of their clinical condition. Previous large studies in pre-, peri and postmenopausal women also reported a positive correlation between circulating androgen levels and CVD risk.[15 38 39] We observed a linear association between FAI and cardiometabolic features in all study groups. A linear association would indicate that women with the lowest androgen concentrations exhibit the most favorable cardiometabolic profile. However, in the current study, POI women exhibited the lowest androgen concentrations compared to other study groups, and POI has been repeatedly associated with an increased CVD risk.[24 40] These findings would correspond more with a U-shaped association between androgens and CVD with increased risk at both ends, as previously proposed.[5 7] This apparent discrepancy may be explained by variations in other biological factors contributing to CVD risk (e.g. circulating estrogen levels) or differences in study type, design and sample size. Moreover, it is noteworthy that the cardiometabolic characteristics of women with POI and PCOS already approximate those of NM women although these women are nearly 20-30 years older. This emphasizes the importance of performing a cardiometabolic evaluation in women diagnosed with PCOS as well as POI.[41 42]

Aside testosterone, endogenous estrogen levels have also been extensively studied as a potential predictor of CVD risk. Circulating estradiol and testosterone are both bound to SHBG, although the binding affinity of SHBG for testosterone is higher than that for estradiol.[43] Increasing SHBG levels, with steady estradiol/testosterone levels, therefore result in a relative increase in the bioactive fraction of estradiol compared with testosterone.[44] Bearing this interactive relation in mind, we performed a post-hoc analysis in which we additionally adjusted the associations between FAI and cardiometabolic abnormalities for endogenous estradiol levels. We found that the observed associations between FAI and lipid metabolism were slightly attenuated. However, in the BMI adjusted models, we did not find any significant changes in the associations between FAI and cardiometabolic features after additional adjustment for estradiol levels (data not shown). These results are in line with previous reported effects of estrogens on lipid metabolism and body fat distribution in women. Estradiol is known to influence the size and number of subcutaneous adipocytes and attenuates lipolysis, which may cause postmenopausal women to gain body fat after menopause.[45 46]

BMI exerted a distinct effect on the observed associations between FAI and cardiometabolic features in our study. After adjustment for BMI, FAI remained significantly associated with most cardiometabolic features in PCOS women. However, in NM women, only glucose metabolism parameters remained associated with FAI after adjustment for BMI, whereas in women with POI, there we no longer any significant associations. It has been proposed that the association between androgens and BMI is modulated through obesity-related changes in circulating levels of insulin and IGF-1.[47 48] Increasing BMI results in a concomitant rise in insulin levels, which inhibits the hepatic production of SHBG and therefore leads to higher levels of bioactive testosterone.[49] Furthermore, insulin and IGF-1 directly stimulate the ovarian synthesis of androgens.[48] Adipose tissue is also able to actively produce androgens through activity of 17beta-hydroxysteroid dehydrogenase.[50] Increased enzyme activity occurring with obesity might further attribute to androgen excess.

One of the strengths of this study is that we measured androgen levels with LC-MS/MS, which is currently considered the gold standard for androgen assessment in women.[51 52] Furthermore, by selecting four distinct groups of women, we were able to study associations between androgen concentrations and cardiometabolic features in women with contrasting endocrine profiles, which, as such, has not been previously performed. Since this study provided abundant data, we presented selected data based on clinical/scientific relevance in order to restrict the number of performed comparisons.

A limitation of the current study is the lack of cardiometabolic features of RC women. Therefore, we were unable to directly compare associations between androgens and cardiometabolic features between these women and the other study groups. Another potential limitation is that although the use of FAI to study the unbound fraction of testosterone in women has been validated, it might be less precise than the direct measurement of the unbound fraction of testosterone in serum.[51] However, we solely used the FAI to study associations between androgens and cardiometabolic features, and did not attempt to establish absolute normative values of free circulating androgen concentrations in different groups of women for clinical usage outside the current study.

The association between sex hormone levels, cardiometabolic abnormalities and the development of actual cardiovascular events in women has not been clearly established yet. Results from the few available long term follow-up studies in the general female population report either no independent relationship between endogenous sex hormone levels and CVD events or only suggest a potential role for testosterone.[5 53 54] The potential association between ovarian dysfunction and future CVD events also remains partially unsettled. In a recent meta-analysis, POI was found to be an independent modest risk factor for ischemic heart disease and overall CVD, but not for stroke.[24] The association between PCOS and cardiometabolic abnormalities (e.g. obesity, dyslipidemia, insulin resistance) has indeed been clearly established. However, previous reports on the actual development of CVD events in PCOS women have been inconsistent.[55-58] Many of these studies suffer from several limitations, such as a retrospective design, unclear phenotyping, limited follow-up, all of which hinder the interpretation of reported results. Unfortunately, due to the cross-sectional design of our study, we were not able to assess the potential relation between androgen levels and the development of actual cardiovascular events.

CONCLUSIONS

In summary, this study demonstrates that androgens intrinsically affect the cardiometabolic features of women with and without various forms ovarian dysfunction. Increased androgen levels were strongly associated with impaired cardiometabolic features in all women participating in the current study. Differences in androgen levels between pre- and postmenopausal women were no longer significant after correcting for age, which indicates that predominantly chronological ageing rather than ovarian ageing influences variations in circulating androgen levels. Furthermore, we observed a substantial effect of BMI on circulating androgen levels. This study affirms the potent effect of androgens on cardiometabolic features, implying that androgens should indeed be regarded as important denominators of women's health. Future research, regarding the role of androgens in the development of CVD and potential modulatory effects of BMI, is required.

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Author contributions

NMP Daan and L Jaspers have contributed to the design of the study, the acquisition, analysis and interpretation of data, drafting and revising of the manuscript and have given final approval of the version to be published. MPH Koster and YB de Rijke have contributed to study design, acquisition of data, drafting and revising of the manuscript and have given final approval of the version to be published. OH Franco and M Kavousi have contributed to the analysis and interpretation of data, drafting and revising of the manuscript and have given final approval of the version to be published. JSE Laven and FJM Broekmans have contributed to the design of the study, interpretation of data, drafting and revising of the manuscript and have given final approval of the version to be published. BCJM Fauser has contributed to the conception and the design this study design, the interpretation of data, drafting and revising of the manuscript and has given final approval of the version to be published.

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Supplemental material

Supplemental material related to this article can be found online at *http://humrep.oxfordjournals.org/content/suppl/2015/08/11/dev195.DC1.*

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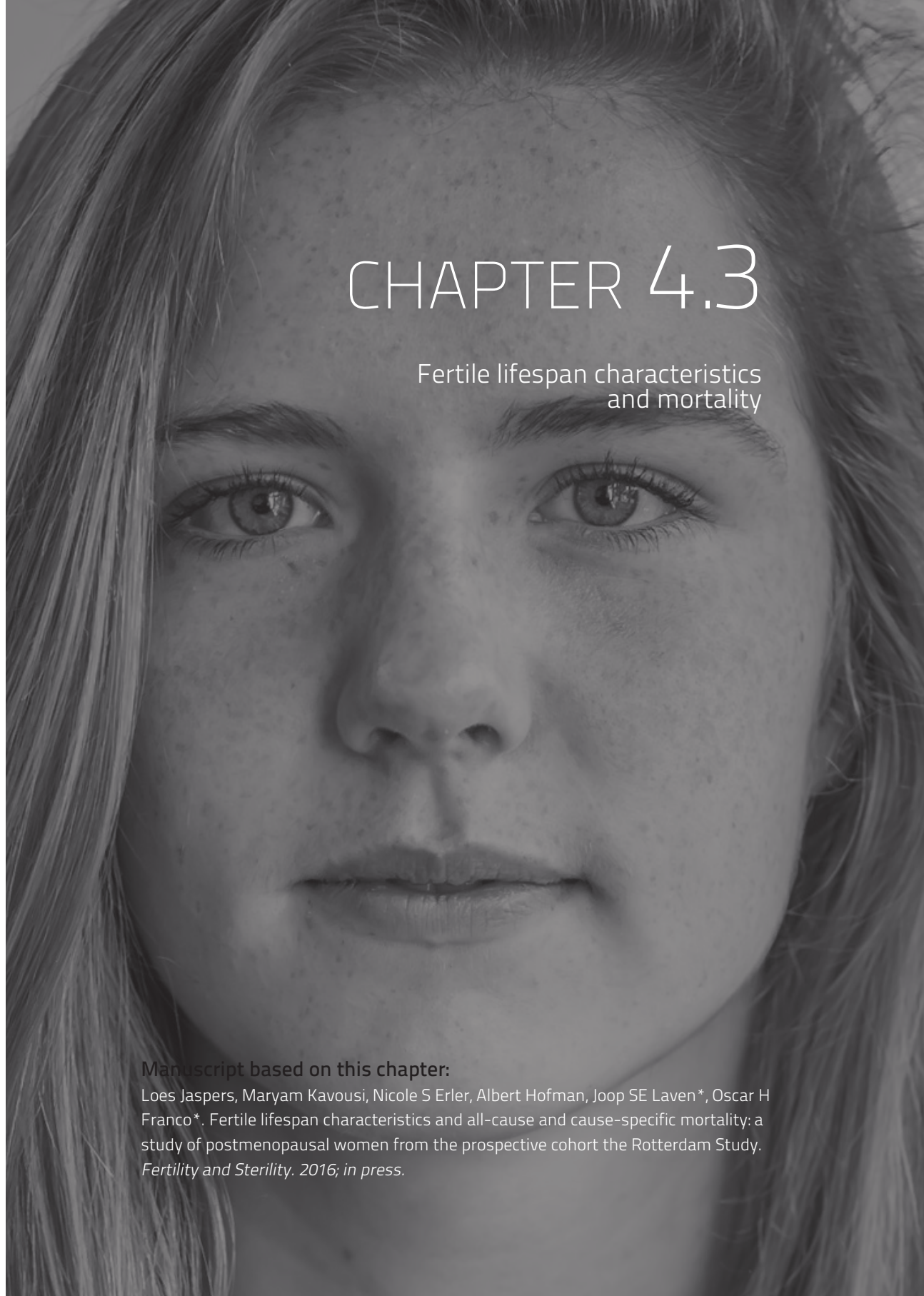


CHAPTER 4.3

Fertile lifespan characteristics and mortality

Manuscript based on this chapter:

Loes Jaspers, Maryam Kavousi, Nicole S Erler, Albert Hofman, Joop SE Laven*, Oscar H Franco*. Fertile lifespan characteristics and all-cause and cause-specific mortality: a study of postmenopausal women from the prospective cohort the Rotterdam Study. *Fertility and Sterility. 2016; in press.*

ABSTRACT

Objectives:
To characterize the relation between established and previously unexplored characteristics of the fertile life with all-cause and cause-specific mortality.

Design, setting, and participants:
A total of 4076 postmenopausal women of the prospective population-based Rotterdam Study, the Netherlands.

Main exposure measures:
Women's fertile lifespan (age at menarche to menopause), number of children, maternal age at first and last child, maternal lifespan (interval between maternal age at first and last child), post-maternal fertile lifespan (interval between age at last child and menopause), lifetime cumulative number of menstrual cycles, and unopposed cumulative endogenous estrogen exposure.

Main outcome measures:
Registry-based all-cause and cause-specific mortality.

Results:
A total of 2754 women died during 14.8 years of follow-up. Compared to women with 2-3 children, a 12% higher hazard of dying was found for women having 1 child (hazard ratio (95% confidence interval), 1.12 (1.01 to 1.24)), which became non-significant in models adjusted for confounders (1.08 (0.96 to 1.21)). Late age at first and last birth were associated with a 1% lower hazard of dying (0.99 (0.98 to 1.00)). Longer maternal and post-maternal fertile lifespan (1.01 (1.00 to 1.02)), longer fertile lifespan (1.02 (1.00 to 1.05)) and unopposed cumulative estrogen exposure (1.02 (1.00 to 1.04)) were significantly harmful for all-cause mortality. Findings differed with regard to direction, size, and statistical significance when stratifying for CVD, cancer, and other mortality.

Conclusions:
Overall, we found that late first and last reproduction were protective for all-cause mortality, whereas a longer maternal lifespan, post-maternal fertile lifespan, and estrogen exposure were harmful for all-cause mortality. More research is needed in contemporary cohorts with larger sample sizes and more extreme ages of birth.

Keywords:
fertility, longevity, mortality

INTRODUCTION

During the past decades there has been a major interest in the role of fertility characteristics, including parity and timing of childbirth, in later life health.[1] This research area has intensified during the past twenty years given the demographic trends wherein couples tend to postpone childbirth to later life stages.[2] Since the 1970s, the proportion of European women aged 30 years and older at first childbirth increased from 8 to 40% and the mean age hereof increased by 4 to 5 years.[3] The paradigm shift in reproductive choices is not without risk as it could lead to involuntary childlessness and unattained desired family sizes.[4] Moreover, pregnancy complications and maternal mortality rates are higher during late motherhood at advanced ages.[5] Nevertheless, benefits from these changing fertility patterns on mortality and longevity have also been widely observed.[1]

Several measures of fertility potential have been suggested, some of which include late reproduction, parity, and age of menopause.[6] The fertile lifespan (the interval between menarche and menopause), which has been used as a proxy for endogenous sex steroid exposure in cardiometabolic studies,[7] could serve as physiologic index for fertility capacity.[8 9] Additionally, since most women don't utilize their entire reproductive period to bear children, it may be of interest to look at more precise measures of the child bearing potential via extra characteristics, which include maternal lifespan (the interval between age at first birth and age at last birth) and post-maternal fertile lifespan (the interval between age at last child and age of menopause).

The full spectrum of fertile lifespan characteristics in association with all-cause or cause-specific mortality has not been examined. Particularly for several characteristics such as age at last birth in relation to cause-specific mortality, the evidence is limited. In the current study we cover a range of established and previously unexplored characteristics of the fertile lifespan and expand the scope from all-cause to cause-specific mortality. Hence, we aimed to assess the associations between eight characteristics of the fertile lifespan (number of children, age at first birth, age at last birth, maternal lifespan, post-maternal fertile lifespan, fertile lifespan itself, lifetime cumulative number of menstrual cycles, and lifetime unopposed endogenous estrogen exposure) with all-cause and cause specific mortality in the prospective population-based Rotterdam Study.

METHODS

Study population
The study was embedded within a prospective, population-based cohort study among subjects 55 years and older in the municipality of Rotterdam, the Netherlands: the Rotterdam Study. The rationale and study design have been described in detail elsewhere.[10]

The baseline examination was completed between 1990 and 1993 (RS-I). Of the 4878 women enrolled in the RS at baseline, 4076 postmenopausal women were included in the present study. Women without informed consent (n=187), missing data in more than 50% of the covariates (n=123), missing age of menarche or menopause (n=473) or missing age at first birth, last birth or number of children (n=19) were excluded from the analyses. An overview of the participant flow can be found in the flowchart (*Supplemental Figure 1*). The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC and by the Ministry of Health, Welfare and Sport of the Netherlands, implementing the Wet Bevolkingsonderzoek: ERGO (Population Studies Act: Rotterdam Study). All participants provided written informed consent to participate in the study and to obtain information from their treating physicians.

Assessment of fertile lifespan characteristics

The self-reported number of children, age of the mother at first and last birth, and age at menarche and menopause were assessed during the baseline interview using a questionnaire. Age at menopause was defined in retrospect as the age at final menstrual period, after a 12-month period of amenorrhoea.[11]

Maternal lifespan was defined as the interval between maternal age at first and last birth in women that had 2 or more children, and may be a more precise measure of the childbearing period compared to the fertile lifespan, considering the fact that women don't utilize the entire fertile period to bear children. The post-maternal fertile lifespan was made by subtracting maternal age at last birth from age of menopause. Both age of menopause and age at last birth could be considered indirect proxies for fertility.[6] Fertile lifespan in years was calculated by subtracting age at menarche from age at menopause. Lifetime cumulative number of menstrual cycles was calculated by subtracting 9 months for each pregnancy, 4 months of breastfeeding for every born child,[12,13] and contraceptive use duration in months from the reproductive lifespan in months. This value, the cumulative endogenous estrogen exposure, was then converted to years, after which it was multiplied by the reported mean number of menstrual cycles per year.[12,14] To get the unopposed cumulative endogenous estrogen exposure, the total postovulatory period in months (i.e. (lifetime number of menstrual cycles*2)/4), was subtracted from the cumulative endogenous estrogen exposure in months.[12]

Assessment of all-cause and cause-specific mortality

Mortality data was obtained via several complementary approaches in order to ascertain (cause of) death for all participants of the Rotterdam Study. Data sources included the central registry of the Municipality of Rotterdam, records from collaborating general practitioners, and information obtained during follow-up rounds. If the vital status of participants was missing, the Central Registry of Genealogy of the Netherlands was consulted. Two research physicians independently classified the cause of death according to the International Classification of Diseases, 10th revision (ICD-10), [15] from which cause-specific mortality was assessed. In case of disagreement, consensus was sought in a separate session. All causes of death were approved by experienced field-specific experts for final classification. For all-cause mortality participants were followed until March 3rd 2015 and for cause-specific mortality until January 1st 2013. For the study of cause-specific mortality, we created 3 groups: cardiovascular mortality, cancer mortality, and other deaths (*Supplemental Methods Section*).

Assessment of covariates

Socio-economic and environmental conditions and family planning can greatly impact the potential biological association between fertility and mortality.[6] Therefore, the following covariates were considered for inclusion in the statistical models: baseline age, education level, marital status, household income, ethnicity, smoking, alcohol intake, diet, physical activity, hormonal contraceptive use, female hormone use, prevalent chronic disease, cycle regularity at age of 25 years, menopause type, and waist to hip ratio. Moreover, women of the same age can have different ages of menopause. Timing of menopause is associated both with fertile lifespan characteristics and with postmenopausal health.[16] Hence, time since menopause was included as a covariate in statistical models. All covariates were self-reported, except for body mass index and waist to hip ratio, which was measured by research assistants at the study centre. A description of the definitions and coding of all covariates can be found in the *Supplemental Methods Section*.

Statistical analysis

As a first step the distributions of all fertile lifespan characteristics was assessed. Since all of these variables were approximately normally distributed, no transformation was necessary. The correlations between the variables number of children, age of the mother at first and last birth, and age at menarche and menopause (the variables used to make the 8 fertile lifespan characteristics), were assessed using the Pearson's correlation coefficient.

The association between the eight fertile lifespan characteristics (all analysed continuously) and all-cause and cause-specific mortality were assessed using cox regression. P-splines were used to characterize the shape of the effect of each continuous exposures with all-cause mortality and to identify any potential non-linear associations.[17] In addition, fertile lifespan characteristics were analysed categorically using categories adapted from literature; if no evidence-based categorizations were available, quartiles were used.[18-21] The proportional hazards assumption was checked by testing the significance of the interaction term of each exposure with time in the cox models (e.g. time*number of children), and this assumption held for all exposures.

Model 1 was adjusted for age and time since menopause. Model 2 was additionally adjusted for education level, marital status, household income, hormonal contraceptive use, smoking, alcohol intake, physical activity, menopause type, female hormone use, prevalent chronic disease, and waist to hip ratio. These covariates were chosen since they were statistically associated with both the exposure (i.e. fertile lifespan characteristic)

and the outcome (mortality) at $\alpha<0.2$.[22] The same models were created for all-cause and cause-specific mortality.
Covariates were imputed using fully conditional specification using the Markov chain Monte Carlo method (n=5 imputations).

Two prespecified interactions were tested in model 2: age*exposure (e.g. age*age at last child) and number of children*exposure (e.g. number of children*age at last child). If the interaction term was significant, the analyses were stratified to show potential differential effects.

As a sensitivity analysis, a complete case analysis was performed to assess whether the imputation process influenced the findings. Furthermore, in a second sensitivity analysis, the population was restricted to women who never used hormonal contraceptives, in order to assess the magnitude of the effect of family planning behaviour through fertility control.23 Moreover, in a third sensitivity analysis, we restricted the population to healthy individuals by means of excluding all women with prevalent chronic disease at baseline or women who died within the first 3 years after baseline (these women may have underlying unknown chronic diseases).

RESULTS

Descriptive statistics

An overview of the study characteristics can be found in *Table 1*. Women had a median age of 69.1 years (interquartile range (IQR) 62.2 to 76.6) and most women were of Northern European descent (98.4%). The median number of children women gave birth to was 2 (IQR 1 to 3) and the mean age at first and last birth were 26.4 (standard deviation (SD) 4.5) and 32.1 (SD 5.5) years, respectively.
During the study period, 2754 women died of any cause and the median follow-up time was 16.6 years (IQR 9.0 to 21.0). Until January 1st, 2013, 780 women died of cardiovascular disease, 547 women of malignant cancers, and 1024 of other causes (*Supplemental Table 1*).
All variables from which the fertile lifespan characteristics were derived were significantly correlated with each other, except for age at menarche, which was only correlated with age at last birth (*Supplemental Table 2*).

Maternal characteristics

The Cox regression results for the association between fertile lifespan characteristics and all-cause mortality can be found in *Table 2*. Compared to the reference group of women with 2 or 3 children, a 12% higher hazard of dying was found for women having 1 child in model 1 (hazard ratio (HR) (95% confidence interval (95% CI)), 1.12 (1.01 to 1.24)), which became statistically non-significant in model 2 (1.08 (0.96 to 1.21)). A 1 year increase in

Table 1. Characteristics of the study population (n=4076).

General characteristics		Value
Age, years	Median (IQR)	69.1 (62.2 to 76.6)
Time since menopause, years	Mean (SD)	21.2 (10.7)
Waist to hip ratio	Mean (SD)	87.1 (8.9)
Body mass index	Mean (SD)	26.7 (4.0)
Education	Number (%)	
Primary		1230 (30.2%)
Lower/intermediate or lower vocational		1873 (45.9%)
Intermediate vocational or higher general		812 (19.9%)
Higher vocational or university		161 (4.0%)
Marital status, living with partner	Number (%)	2087 (51.2%)
Equivalent household income (/1000,-)	Median (IQR)	1.8 (1.2 to 2.5)
Ethnicity, Caucasian	Number (%)	4011 (98.4%)
Menopause type, natural	Number (%)	3827 (93.9%)
Oral contraceptive use, yes	Number (%)	1172 (28.7%)
Female hormone use, yes	Number (%)	544 (13.3%)
Prevalent chronic disease, yes	Number (%)	629 (15.4%)
Coronary heart disease		176 (4.4%)
Heart failure		137 (3.4%)
Stroke		89 (2.2%)
Diabetes Mellitus		206 (5.1%)
Cancer		28 (2.3%)
COPD		104 (2.6%)
Smoking, current	Number (%)	752 (18.4%)
Alcohol intake, glasses/day	Median (IQR)	0.1 (0 to 0.7)
Physical activity, ideal levels[a]	Number (%)	3655 (89.7%)

Table 1. Continued

Fertile lifespan characteristics		Value
Number of children	Median (IQR)	2 (1-3)
Number of children	Number (%)	
0 children		845 (20.7%)
1 child		665 (16.3%)
2 children		1141 (28.0%)
3 children		743 (18.2%)
4 children		383 (9.4%)
5 or more children		299 (7.3%)
Age at first birth, years	Mean (SD)	26.4 (4.5)
Age at first birth	Number (%)	
19 years or younger		166 (5.1%)
20-24 years		1166 (36.1%)
25-34 years		1745 (54.0%)
35 years or older		154 (4.8%)
Age at last birth, years	Mean (SD)	32.1 (5.5)
Age at last birth	Number (%)	
24 years or younger		335 (10.4%)
25-34 years		1880 (58.2%)
35-39 years		743 (23.0%)
40 years or older		273 (8.4%)
Maternal lifespan, years	Median (IQR)	5.0 (2.0 to 9.0)
Post-maternal fertile lifespan, years	Mean (SD)	16.8 (7.0)
Fertile lifespan, years	Mean (SD)	35.2 (5.3)
Lifetime number of menstrual cycles	Mean (SD)	331.4 (106.4)
Unopposed cumulative endogenous estrogen exposure, years	Median (IQR)	16.1 (12.8 to 18.6)

[a] ≥150 / ≥75 minutes/week of moderate and/or vigorous activity.
COPD=chronic obstructive pulmonary disorder, IQR=interquartile range, SD=standard deviation.

Table 2. Association between fertile lifespan characteristics and all-cause mortality.

	N	Events	Model 1		Model 2	
			HR (95%CI)	p-value	HR (95%CI)	p-value
Number of children (continuous)	4076	2754	1.00 (0.98 to 1.02)	0.83	1.00 (0.97 to 1.02)	0.76
Number of children (categorical)						
0 children	845	602	1.06 (0.96 to 1.17)	0.24	1.10 (0.98 to 1.23)	0.10
1 child	665	470	**1.12 (1.01 to 1.24)**	**0.04**	1.08 (0.96 to 1.21)	0.20
2 or 3 children	1884	1194	Reference		Reference	
4 or more children	682	488	1.06 (0.95 to 1.17)	0.32	1.07 (0.95 to 1.19)	0.28
Age at first birth (continuous)	3231	2152	**0.99 (0.98 to 1.00)**	**0.003**	**0.99 (0.98 to 1.00)**	**0.01**
Age at first birth (categorical)						
19 years or younger	166	114	1.19 (0.98 to 1.44)	0.08	1.09 (0.89 to 1.35)	0.41
20-24 years	1166	740	1.01 (0.92 to 1.10)	0.89	0.99 (0.89 to 1.09)	0.78
25-34 years	1745	1188	Reference		Reference	
35 years or older	154	110	**0.79 (0.65 to 0.96)**	**0.02**	**0.75 (0.61 to 0.93)**	**0.01**
Age at last birth (continuous)	3231	2152	**0.99 (0.98 to 1.00)**	**0.04**	0.99 (0.98 to 1.00)	0.14
Age at last birth (categorical)						
24 or younger	335	233	1.15 (1.00 to 1.32)	0.06	1.17 (1.00 to 1.36)	0.05
25-34 years	1880	1150	Reference		Reference	
35-39 years	743	554	0.99 (0.90 to 1.10)	0.90	0.99 (0.89 to 1.11)	0.87
40 years or older	273	215	0.97 (0.84 to 1.13)	0.69	1.01 (0.85 to 1.19)	0.95

Table 2. Continued

	N	Events	Model 1		Model 2	
			HR (95%CI)	p-value	HR (95%CI)	p-value
Maternal lifespan, years	2566	1668	**1.01 (1.00 to 1.02)**	**0.05**	1.01 (1.00 to 1.02)	0.14
Post-maternal fertile lifespan, years	3231	2152	**1.01 (1.00 to 1.02)**	**0.04**	1.01 (1.00 to 1.02)	0.14
Fertile lifespan, years	4076	2754	**1.02 (1.00 to 1.04)**	**0.04**	**1.02 (1.00 to 1.05)**	**0.04**
Lifetime number of menstrual cycles	1755	928	1.00 (1.00 to 1.00)	0.15	1.00 (1.00 to 1.00)	0.27
Unopposed cumulative endogenous estrogen exposure, years	1736	913	1.01 (0.99 to 1.03)	0.24	1.02 (1.00 to 1.04)	0.06

Model 1 was adjusted for age and time since menopause.
Model 2 was additionally adjusted for education level, marital status, household income, oral contraceptive use, smoking, alcohol intake, physical activity, menopause type, female hormone use, prevalent chronic disease, waist to hip ratio, and body mass index.
CI=confidence interval, HR=hazard ratio, N=number.

age at first birth was associated with a 1% lower hazard of dying in model 1 and 2 (0.99 (0.98 to 1.00)). When compared to the reference group of women giving birth between 25 to 34 years, older women (i.e. ≥35 years) had a 25% lower hazard of dying in model 2 (0.75 (0.61-0.93)). For age at last birth, a 1 year increase was associated with a 1% lower hazard of dying in model 1 (0.99 (0.98 to 1.00)). A 1 year longer maternal and post-maternal fertile lifespan was significantly associated with a 1% higher hazard of dying in model 1 (1.01 (1.00 to 1.02) for both), but lost significance in model 2.

Some differences were observed when comparing the association of fertile lifespan characteristics with cause-specific mortality to the association with all-cause mortality (*Supplemental Table 3-5*).
For number of children, having no children compared to having 2 to 3 children was associated with a 26% higher hazard for CVD mortality (1.26 (1.02 to 1.56)). Late age at first birth (25 years or older) resulted in a 16% higher hazard for cancer mortality (1.16 (0.94 to 1.46)), whereas this was associated with a 15% lower hazard for other mortality (0.85 (0.73 to 0.99)). Late age at last birth (35 years or older) resulted in a 17% lower hazard for CVD mortality (0.83 (0.68 to 1.00)), whereas no effect was found for the other causes of death.

Proxies for estrogen exposure

A 1 year longer fertile lifespan was associated with a 2% higher hazard for all-cause mortality in model 1and model 2 (1.02 (1.00 to 1.05)). The observed effects were similar for unopposed cumulative endogenous estrogen exposure. No associations were found between lifetime number of menstrual cycles and all-cause mortality (*Table 2*).

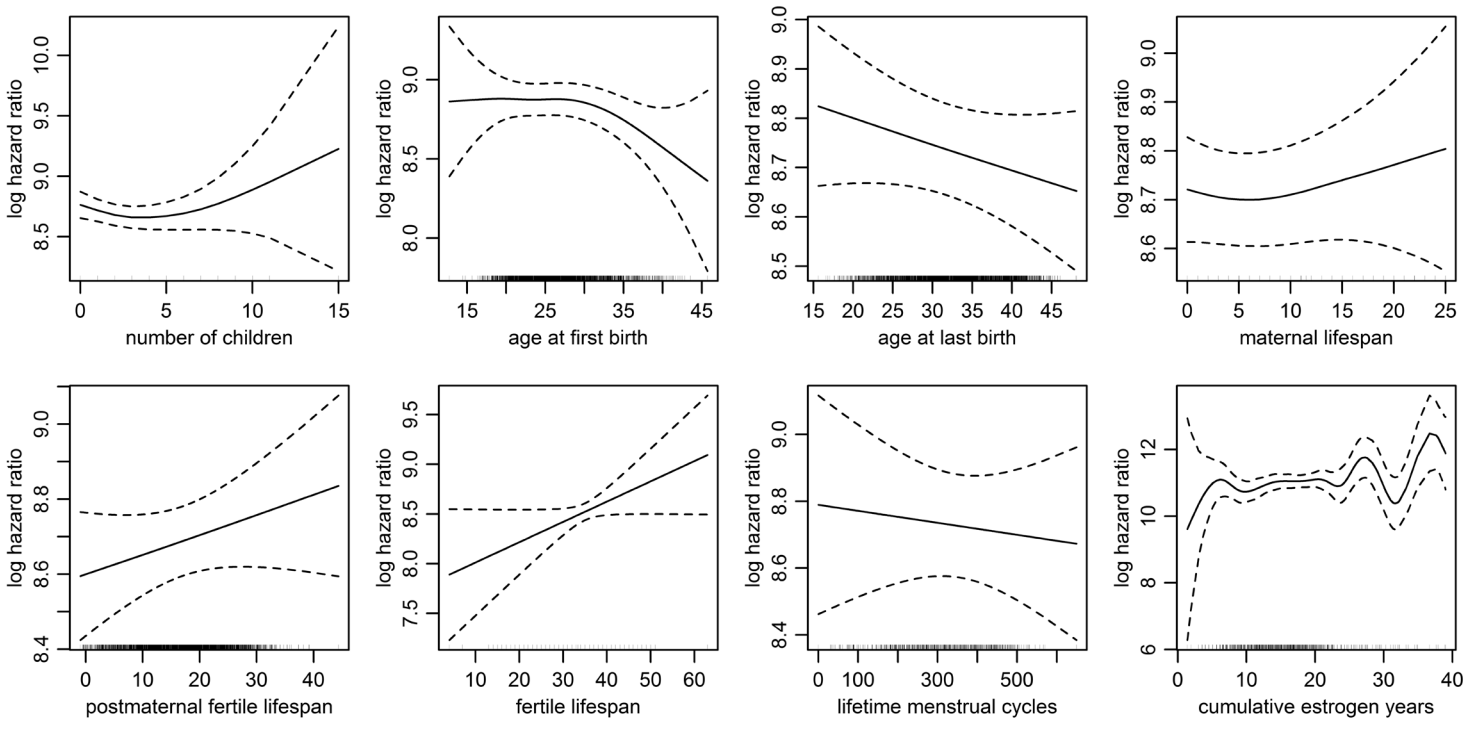
Fertile lifespan and unopposed cumulative endogenous estrogen exposure were associated with a 5% and 4% higher hazard for CVD mortality (1.05 (1.00 to 1.10) and 1.04 (1.00 to 1.09), respectively), but not with cancer and other mortality (*Supplemental Table 3-5*). A larger number of lifetime number of menstrual cycles was significantly associated with other mortality, although the effect size reflected unity (1.00 (1.00 to 1.00)); *Supplemental Table 5*.

Linearity and interaction terms

In *Figure 1* the shape of the effects for each fertile lifespan characteristic and all-cause mortality are shown. There was evidence against linearity only for number of children (p-values for each imputed set ranged from 0.0073 to 0.0192), for which the association was J-shaped.

The interaction terms with baseline age were not significant for any of the fertile lifespan characteristics, whereas the interaction terms with number of children were significant for age at last birth (p-value=0.03), post-maternal fertile lifespan (p-value=0.03), and cumulative estrogen exposure (p-value=0.04). When stratifying the analysis for 0, 1, 2

Figure 1. The shape of the log hazard ratio of each fertile lifespan characteristic using p-splines.



The solid line represents the estimated log hazard ratio of each fertile lifespan characteristic; the dashed lines represent the 95% confidence intervals. Cumulative estrogen years=unopposed cumulative endogenous estrogen exposure in years.

Table 3. Association between fertile lifespan characteristics and all-cause mortality, stratified for number of children.

	0 children (n=845)		**1 child (n=665)**		**2 or 3 children (n=1884)**		**4 or more children (n=682)**	
	HR (95%CI)	**p-value**	**HR (95%CI)**	**p-value**	**HR (95%CI)**	**p-value**	**HR (95%CI)**	**p-value**
Age at last birth (continuous)	NA		**0.97 (0.95 to 0.99)**	**0.003**	1.00 (0.99 to 1.02)	0.82	1.00 (0.98 to 1.02)	0.85
Age at last birth (dichotomous)	NA							
34 years or younger	NA		Reference		Reference		Reference	
35 years or older	NA		**0.63 (0.46 to 0.85)**	**0.003**	1.06 (0.92 to 1.22)	0.43	0.98 (0.80 to 1.21)	0.85
Post-maternal fertile lifespan, years	NA		**1.03 (1.01 to 1.05)**	**0.003**	1.00 (0.99 to 1.01)	0.82	1.00 (0.98 to 1.03)	0.85
Unopposed cumulative endogenous estrogen exposure, years	1.02 (0.95 to 1.10)	0.54	**1.08 (1.03 to 1.13)**	**0.002**	1.01 (0.98 to 1.04)	0.62	1.00 (0.95 to 1.04)	0.82

The presented results are adjusted for the covariates from model 2: age, time since menopause, education level, marital status, household income, oral contraceptive use, smoking, alcohol intake, physical activity, menopause type, female hormone use, prevalent chronic disease, waist to hip ratio, and body mass index.
CI=confidence interval, HR=hazard ratio, N=number, NA=not applicable.

or 3, and 4 or more children, we found that the associations were merely evident for the group of women bearing 1 child for age at last birth (0.97 (0.95 to 0.99), p-value=0.003), for post-maternal fertile lifespan (1.03 (1.01 to 1.05), p-value=0.003), and for endogenous estrogen exposure (1.08 (1.03 to 1.13), p-value=0.002), whereas no significant associations were found for the other 3 groups (*Table 3*).

Supplemental Table 6 details the multiple imputation process. In 3 different sets of sensitivity analyses; the complete case analyses, the analyses restricted to the non-diseased population, and the analyses excluding women ever using oral contraceptives, the direction, size, and significance of the associations remained the same (data not shown). Finally, since of the 4878 women enrolled in the RS at baseline, 4076 postmenopausal women were included in the present study, we compared the characteristics of the included participants to the total population of women at baseline. Compared to the total female population of the Rotterdam Study, women included in this study were 0.8 years younger, and had 0.6% less prevalent chronic disease, but did not differ for other baseline characteristics (*Supplemental Table 7*).

DISCUSSION

Given the demographic changes in reproductive choices and their relevance for mortality and longevity, we characterized the relation between established and previously unexplored characteristics of the fertile life with mortality, and therein expanded the scope from all-cause to cause-specific mortality. Overall, we found that late first and last reproduction were protective for all-cause mortality, whereas a longer maternal lifespan, post-maternal fertile lifespan, and estrogen exposure were harmful for all-cause mortality. For late last reproduction, post-maternal fertile lifespan, and estrogen exposure, these findings were merely evident in 1-child mothers. In addition, the findings differed with regard to direction, size, and significance when stratifying for CVD, cancer, and other mortality. From a clinical perspective, the magnitude of the associations ranged from a 1-5% lower or higher risk of dying per year increase of each fertile lifespan characteristic.

Strengths and limitations

Strengths of this study included the consideration of the full spectrum of established as well as previously unexplored characteristics of the fertile lifespan, and access to the precise adjudicated causes of death information, which allowed us to study cause-specific mortality. Furthermore, the contemporary character of the cohort, in contrary to historical cohorts, provides a valuable insight into the role of fertility in longevity against a background of increasing reproductive choices and improved standards of care and therefore is applicable to the present time. Additionally, the adjustment for many confounders, the graphical representation of the effects using p-splines, and the stratified analysis for number of children, adds new information to the existing body of evidence in this field of work.

Several limitations merit careful consideration. Although we had information on marital status, no information was available on age at marriage and number of marriages. Furthermore, for the included women we had no information on fetal losses, abortions, and stillbirths. Assumptions were made for assembling the lifetime cumulative number of menstrual cycles and unopposed cumulative estrogen exposure. Since fertile lifespan characteristics were assessed when women already reached menopause, retrospective recall could have occurred. However, because information on fertile lifespan characteristics were collected before the outcome (mortality) occurred, we reasonably do not expect this recall to have impacted our findings. Also, the Rotterdam Study comprises of men and women of 55 years and older. Hence, immortal time bias could have occurred, given that women could have died during their reproductive life, for instance of maternal complications, and would therefore not be included in the studied population.[24] However, even if occurred, this would have led to an underestimation of the true effects in our study. Lastly, fertility characteristics may be of different importance for disease subtypes, such as breast, colorectal, and lung cancer. Our study was underpowered to stratify analyses for different disease and cancer subtypes.

Comparison with other studies and possible explanations

When comparing our findings to other studies, it is important to consider that the Rotterdam Study is a contemporary cohort and therefore conclusions with regard to natural fertility are limited. In contrast to historical cohorts from the 18th and 19th century where fertility followed pre-contraceptive patterns, in the current cohort there could have been a larger impact of reproductive choices. Among the included women, the youngest women were 27 years old at the time of the introduction of the first oral contraceptive in the Netherlands in 1962, and only 30% of women indicated ever using oral contraceptives.[25] (25) (24) The mean age at first birth in our study was 26 years, meaning that the influence of contraceptive use was probably less pronounced for age at first birth, compared to the consecutive births thereafter. Indeed, this may be supported by the large post-maternal fertile lifespan found in this study (17 years) indicating women stopped reproducing long before the onset of menopause. Where age of last birth may be influenced by family planning, economic circumstances and socially acceptable propagation habits, age of menopause is less subject to these external factors.[6] The interval between the two, i.e. post-maternal fertile lifespan, could provide insight in the potential influence of these external factors within our study population. The age at last birth was on average 32 years, whereas last reproduction was nearly 10 years later in historical cohorts.[26] In sensitivity analyses we repeated the analyses excluding women who ever used oral contraceptives. The results did not substantially change with regard to significance, direction, and size of the effect.

Maternal characteristics

In line with our findings, for number of children, contemporary cohorts consistently show a nonlinear effect, with the highest mortality in nulliparous women and women bearing 4 or more children[19 27], whereas the findings from historical cohorts have shown negative, neutral and positive effects.[23 28] For age at first birth, the empirical results are inconsistent, ranging from a beneficial effect of late first birth on longevity to no effect.[1 23] In our study, we found a linear protective effect of late first reproduction on mortality, of which the statistical significance attenuated after adjusting for socio-economic factors and lifestyle. The effects of parity and first reproduction on mortality have been explained before by evolutionary fitness trade-off theories, balancing reproductive investment and somatic maintenance.[29 30] Two of such theories are the antagonistic pleiotropy theory (i.e. the same gene could be beneficial in early life, whereas being detrimental in later life),[31] and the disposable soma theory (i.e. the limited amount of energy has to be divided between reproductive activities and maintaining the soma).[32]

Late first parenthood was protective for other mortality. Whereas early parenthood has been associated with lower socio-economic status, particularly during childhood, and with personality characteristics such as a tendency towards more risk taking behaviour, late parenthood could be characterized by less stress and better career prospects.[33] We would have expected to find the same protective effect for cardiovascular mortality,[33] for which the observed hazard was around unity. We did find a significant protective effect of late last reproduction with cardiovascular mortality, which attenuated after adjustment for covariates.

There has been a particular interest in late last reproduction, since studies from both contemporary and historical cohorts consistently point towards a protective effect of late last childbirth on post-reproductive survival.[1 23] In our study, we found this effect, but less pronounced than in other studies. This could be explained by the fact that only 10 of the included women gave birth to their last child above the age of 45, whereas in other studies these numbers were higher.[18] The shape of the effect of age at last birth was linear and protective for mortality in our study. Although most studies did not comment on this extensively, one study by Helle and colleagues did not find any evidence against linearity for age at last birth, in line with our findings.[1]

There have been several theories about which mechanisms could underlie the protective effect of late last reproduction.[23] Reproductive performance, including measures such as late age of menopause and late last reproduction, could be viewed as a marker for later life health.[21 23 34 35] Studies have shown that that there is a genetic link between fertility and longevity, that encompasses overlapping pathways and genes for telomerase activity, apoptosis mediated through p53/p73, Foxo transcription factors, the expression of APOE, and the role of the immune system, mitochondrial function, and oxidative stress in both processes.[6] Moreover, reproductive performance and longevity have shown to be

linked via common genetic factors related to DNA repair and maintenance. Therefore, it could be that the occurrence of menopause is a consequence of the ageing of the soma that results from the deterioration of these DNA repair mechanisms.
Others have suggested that extended fertility and its association with a longer lifespan might be explained by the 'rejuvenation theory'. This theory describes that late pregnancy, childbirth, and breastfeeding could be rejuvenating at the physiological level[36], and that the presence of young children in the post-reproductive period could extend the lifespan.[37]

Early versus late child bearing

Interestingly, we found a differential effect for age at last birth when stratifying the analysis for number of children. After stratification, the protective effect of late last reproduction (>35 years) on the risk of dying, compared to last child bearing while 34 years or younger, was merely evident among women with one child only. A similar interaction was found in a study by Gagnon and colleagues in a historical context.[38]

For age at first reproduction, the median age was 37.1, 29.3, and 25.4 years in 1-child, 2-3 child and 4 or more child mothers, respectively. The ages at last reproduction were 37.1, 37.5, and 38.7 years, respectively. Since for 1-child mothers the age at first and last reproduction is the same, there is a nearly 8 year difference in first reproductive event between 1-child and > 1 child mothers.

A possible explanation of the observed differential effect may be that 1-child mothers precisely planned when they wanted to have their first child but due to their age may have been unable to attain their desired family size with a second or third child. Some support for this explanation comes from the recent work performed by Habbema and colleagues, that found that in order to have a 90% chance of giving birth to 1 child, a woman should be no older than 35 years, and in order to have 2 children, women should start no later than 31 years.[4] The social factors that caused these women to have their child late may have protected them from dying.[24] Indeed, when looking into the characteristics of these women, we found that older mothers were more highly educated and less often smokers compared to younger mothers.

Proxies for estrogen exposure

The findings for fertile lifespan and unopposed cumulative estrogen exposure were in the same line, both indicating that longer estrogen exposure was hazardous for all-cause mortality, and CVD mortality in particular, whereas no association was found between estrogen exposure and cancer mortality. The latter could be explained by the fact that various subtypes of cancer that were included in the study, including of both hormonal and non-hormonal cancers. Findings from other studies reporting the association between endogenous estrogen levels and cardiovascular outcomes have been inconsistent, particularly in the elderly. Estradiol is supposed to have a protective

role in the cardiovascular system.[39] However, in line with our findings, an increasing number of studies suggest the opposite.[40-47]

Several potential mechanisms have been described. Visceral adiposity, which is associated with inflammation, insulin resistance/diabetes, and atherogenic dyslipidemia is suggested to increase estradiol levels via two pathways. Adiposity is negatively correlated with sex hormone binding globulin, leading to a higher fraction of bioactive estradiol. Also, central adiposity increases aromatase activity, and therefore the conversion of testosterone into estradiol.[44] Higher levels of estradiol were more strongly associated with atherothrombotic stroke in older postmenopausal women with greater central adiposity.[43] In our study, adjusting for waist-hip ratio did not materially change the findings, indicating that pathways beyond adiposity may exist.
Another suggested explanation for this finding comes from the work of Naessen and colleagues.[46 47] They suggest that higher levels of endogenous estrogen do not increase the risk of atherosclerosis, but that that the rise in endogenous estrogen is a response to counteract the developing atherosclerosis.[46 47]

CONCLUSIONS

Overall, we found associations between established and previously unexplored fertile lifespan characteristics and mortality that differed for different causes of death. We found that late first and last reproduction were protective for all-cause mortality, whereas a longer maternal lifespan, post-maternal fertile lifespan, and estrogen exposure were harmful for all-cause mortality. Furthermore, with regard to late last reproduction, differences were found when comparing women with different number of children that could partly be explained by socio-economic status and overdue initiation of family planning. To broaden our understanding of the effect of changing fertility patterns on mortality in the present time, more research is needed in contemporary cohorts with larger sample sizes and more extreme number of children and ages of birth. The findings in contemporary cohorts may differ, due to changes in women's reproductive choices, including use of hormonal contraception. The implications for women with diverse number of children for different causes of death should be further explored, taking into account insights in reproductive choices, and an extensive evaluation of the role of socio-economic status.

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Author contributions

All authors substantially contributed to the conception or design of the work (LJ, JSEL, MK, OHF), or the acquisition (AH), analysis (LJ, NSE), or interpretation (LJ, NSE, JSEL, MK, OHF) of data for the work. LJ drafted the work, and all co-authors critically revised the work for important intellectual content. All authors provided final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring questions related to the accuracy or integrity of any part of the work are appropriately investigated or resolved.
LJ is the guarantor of the work and accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Disclosures

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf and declare: support for the study as described above; LJ reported receiving research support from Metagenics Inc; JSEL has received unrestricted research grants form the following pharmaceutical companies (in alphabetical order): Ferring, Merck Sharpe & Dome (MSD), Merck Serono, Organon, Serono, Schering Plough. MK is supported by the NWO VENI grant (VENI, 91616079). OHF reported receiving grants or research support from Metagenics Inc. NSE and AH have nothing to disclose. No other relationships or activities that could appear to have influenced the submitted work.

Supplemental material

Supplemental material related to this article can be found online at *http://www.fertstert.org/article/S0015-0282(16)63004-2/addons.*

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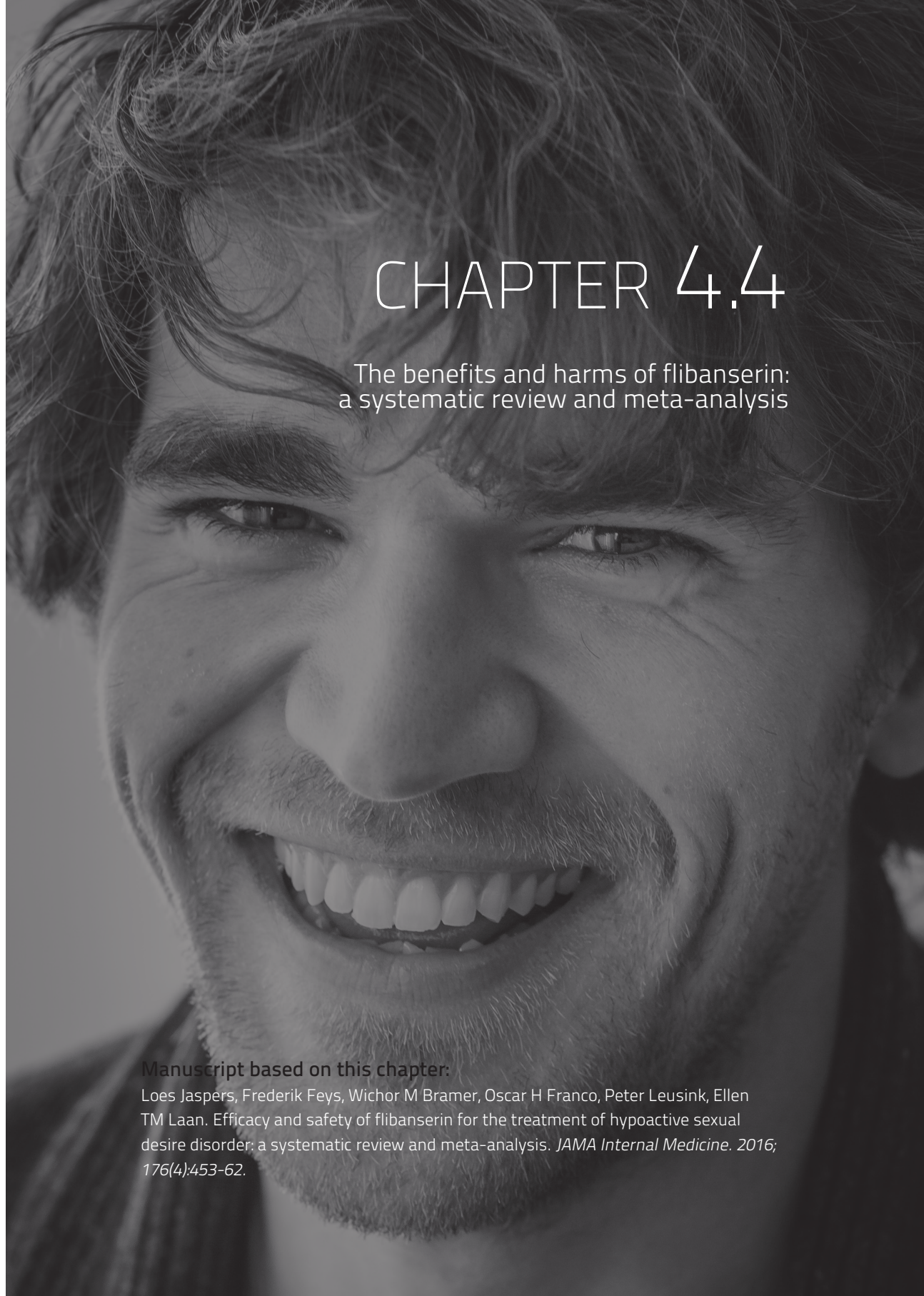


CHAPTER 4.4

The benefits and harms of flibanserin: a systematic review and meta-analysis

Manuscript based on this chapter:

Loes Jaspers, Frederik Feys, Wichor M Bramer, Oscar H Franco, Peter Leusink, Ellen TM Laan. Efficacy and safety of flibanserin for the treatment of hypoactive sexual desire disorder: a systematic review and meta-analysis. *JAMA Internal Medicine. 2016; 176(4):453-62.*

ABSTRACT

Background:

In August 2015 the US Food and Drug Administration (FDA) approved flibanserin as a treatment for hypoactive sexual desire disorder (HSDD) in premenopausal women, despite concern about suboptimal risk-benefit trade-offs.

Objective:

To conduct a systematic review and meta-analysis of randomized controlled trials (RCTs) assessing efficacy and safety of flibanserin for the treatment of HSDD in women.

Data sources:

Medical databases (among others, Embase, Medline, Psycinfo) and trial registries were searched from inception to June 17, 2015. Reference lists of retrieved studies were searched for additional publications.

Study selection:

RCTs assessing treatment effects of flibanserin in pre- and postmenopausal women were eligible. No age, language, or date restrictions were applied. Abstract and full-text selection was done by two independent reviewers.

Data extraction and synthesis:

Data were extracted by one reviewer and checked by a second reviewer. Results were pooled using two approaches depending on the blinding risk of bias.

Main outcome measures:

Primary efficacy outcomes included number of satisfying sexual events (SSE), e-Diary sexual desire, and Female Sexual Function Index (FSFI) desire. Safety outcomes included, among others, 4 common adverse events (AEs): dizziness, somnolence, nausea, and fatigue.

Results:

Five published and 3 unpublished studies including 5914 women were included. Pooled mean differences for SSE change from baseline were 0.49 (95% confidence interval (CI), 0.32 to 0.67) between 100mg flibanserin and placebo, 1.63 (95%CI, 0.45 to 2.82) for e-Diary desire, and 0.27 (95%CI, 0.17 to 0.38) for FSFI desire. The risk ratio for study discontinuation due AEs was 2.19 (95%CI, 1.50 to 3.20). The risk ratio for dizziness was 4.00 (95%CI, 2.56 to 6.27) in flibanserin vs placebo, 3.97 (95%CI, 3.01 to 5.24) for somnolence, 2.35 (95%CI, 1.85 to 2.98) for nausea, and 1.64 (95%CI, 1.27 to 2.13) for fatigue. Women's mean global impression of improvement scores indicated minimal improvement no change.

Conclusions:

Treatment with flibanserin, on average, resulted in half of one additional satisfying sexual event per month, while substantially increasing the risk of dizziness, somnolence, nausea, and fatigue. Overall, the quality of the evidence was graded as very low. Before flibanserin can be recommended in guidelines and clinical practice, future studies should include women from diverse populations, particularly women with comorbidities, medication use, and surgical menopause.

Keywords:

flibanserin, hypoactive sexual desire disorder, efficacy, safety, systematic review, meta-analysis

INTRODUCTION

In August 2015, the US Food and Drug Administration (FDA) approved flibanserin as a medical treatment for hypoactive sexual desire disorder (HSDD) in premenopausal women.[1] Flibanserin, a 5-HT1A agonist, a 5-HT2A antagonist and a very weak partial agonist on dopamine D4 receptors, increases dopamine and norepinephrine and decreases serotonin in animal brain areas.[2 3] Therefore, since dopamine and norepinephrine are thought to promote and serotonin is thought to inhibit sexual desire and arousal,[3 4] it was suggested that flibanserin enhances sexual desire in HSDD.

With prevalences from 10 to 40%, HSDD is defined as "persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity" accompanied by "marked distress and interpersonal difficulty", that is not accounted for by a nonsexual mental disorder, medication, severe relationship stress, or a general medical condition.[5 6] With the appearance of the Diagnostic and Statistical Manual of Mental Disorders (5th edition), HSDD was replaced by female sexual interest/arousal disorder, merging arousal and desire disorders.

The approval of flibanserin at the intersection of science, policy, and advocacy received considerable attention in the public domain and was accompanied by debates among health institutions and stakeholders.[7] Some observed significant benefits without safety concerns,[8] whereas others expressed concern about medicalization of women's sexuality, questioned whether benefits outweighed risks, and expressed concern about pharmaceutical industry influencing FDA's decisions.[9]

Several narrative reviews and commentaries have been published, providing a complete or partial overview of biomedical and integrative treatment options for HSDD.[8 10-17] To our knowledge, no studies have comprehensively summarized the evidence regarding the beneficial and harmful treatment effects of flibanserin for women with HSDD. Therefore, in view of these controversies and the availability of this new prescription drug, we aimed to assess efficacy and safety of flibanserin for the treatment of HSDD in women by performing a systematic review and meta-analysis of randomized controlled trials.

METHODS

Search strategy and inclusion criteria

We conducted a systematic search of 3 trial registries and 13 electronic databases (including Embase.com, Medline (Ovid), and Psycinfo) from inception to June 17, 2015, to identify all studies assessing efficacy and safety of flibanserin for the treatment of women with HSDD. The search strategy for each database was designed by an experienced medical information specialist (*Supplemental Methods 1*).

A stepwise selection procedure was followed (*Supplemental Figure 1*). Eligible studies included interventional studies assessing efficacy and safety of flibanserin in women with HSDD or sexual interest/arousal disorder (*Supplemental Methods 2*). Studies in premenopausal and postmenopausal women were eligible, given the potential off-label use in postmenopausal women.[7] Studies assessing any outcome measure were eligible; outcome measures included, among others, change from baseline in number of satisfying sexual events (SSE), sexual desire, and distress related to desire; adverse events (AEs) leading to study discontinuation; specific AEs including dizziness, somnolence, nausea, and fatigue and serious AEs. No age, language or date restrictions were applied.

Study selection

Two independent researchers reviewed all abstracts and registered trials, and selected potentially eligible studies. Full texts of these studies were retrieved to assess fulfilment of the selection criteria. Disagreements were resolved through consensus or consultation of a third reviewer. The references of the retrieved studies were scanned to identify additional publications that were missed by the initial search.

Data extraction

A data collection form was prepared to extract all relevant information from the included studies. Extracted data included period of surveillance, country, funding source, participant characteristics (age, menopausal status, duration of HSDD, and more), dosage regimens, and participant flow. Furthermore, baseline and end of follow-up levels of the outcomes were extracted. A second researcher checked the extracted data.
In cases of missing data, the clinicaltrials.gov website and the Advisory Committee Briefing Documents were consulted.[18] In 5 cases, we contacted authors and in all cases the owner of flibanserin, Sprout Pharmaceuticals Inc.

Quality evaluation

The quality of the evidence per outcome was graded according to the recommendations of the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group, and included consideration of within-study risk of bias (methodological quality), directness of evidence, heterogeneity, imprecision, and risk of publication bias.[19]
The within-study risk of bias was assessed by two researchers independently using the Cochrane Collaboration risk of bias tool.[19]
Since the number of eligible studies was smaller than 10, assessing publication bias with funnel plots was not feasible.[19]

Efficacy and safety outcomes

Primary efficacy outcomes included number of SSE per month, monthly sexual desire intensity (e-Diary desire; Invivodata Inc), and Female Sexual Function Index desire domain (FSFI desire).[20] Five efficacy outcomes were labelled as secondary: FSFI total

score, Female Sexual Distress Scale-Revised Item 13 and total score,[21] Patient's Global Impression of Improvement, and Patient Benefit Evaluation.
Safety outcomes included any AEs, investigator defined drug-related AEs, AEs leading to study discontinuation, the 4 most common AEs (dizziness, somnolence, nausea, and fatigue), and severe and serious AEs.

Statistical analyses

Heterogeneity permitting, we sought to pool the results of women using 100 milligrams (mg) of flibanserin (100mg once daily at bedtime or 50mg twice daily) vs women using placebo via fixed and random effects models. Heterogeneity was assessed using Cochrane X^2 and I^2 statistics. Random effects models were used in case of clinical heterogeneity (differences in study inclusion criteria) or statistical heterogeneity (I-squared of ≥40% or a significant test for heterogeneity). In all other cases, fixed effects models were used.

Adequately blinded studies (*Supplemental Methods 3*) were summarized using the inverse variance weighted mean difference and 95% confidence interval (CI) for continuous outcomes, and the risk difference or risk ratio and 95% CI for dichotomous outcomes. For inadequately blinded studies, we presented outcomes for flibanserin and placebo groups separately.[22 23]

In case of missing data for the number in analysis or standard error (SE), for efficacy outcomes the number of study completers and the largest outcome-specific SE from the other studies were imputed, respectively; a conservative approach given its modest effect on study size, weighting, and precision estimates. For safety outcomes, the number of study starters was used, given that dropout, among other reasons, was likely to be related to AEs.

We performed 3 subgroup analyses, one in premenopausal women only, a second for the FDA-approved dose of 100mg once daily at bedtime, and a third comparing published and unpublished studies.

In sensitivity analyses, the smallest outcome-specific SE was taken and the number of study completers and study starters were replaced by each other in efficacy and safety assessments, respectively. Furthermore, to detect the influence of a single study on the overall meta-analysis, the studies were omitted 1 by 1.

All statistical data analyses were performed using Stata Statistical Software: Release 12 (StataCorp LP).

RESULTS

Of 592 references and registered trials initially identified, 8 studies were included in the qualitative assessment and 4 to 7 studies were included in the quantitative synthesis, depending on how many studies reported each outcome (*Supplemental Figure 1*). Three studies were unpublished trials conducted between 2006 and 2011 (*Supplemental Table 1*). The remaining 5 studies were published between 2011 and 2014.[24-28]

General characteristics of the included studies

All studies were randomized, double-blind, placebo-controlled trials performed in the United States of America (USA) and Canada, except for 1 study, which was performed in 13 European countries. All studies included premenopausal (6 studies) or postmenopausal women (2 studies) with generalized acquired HSDD according to the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision) and for whom the diagnosis was ascertained by a trained clinician via a diagnostic interview (*Table 1*). No studies were found for women with sexual interest/arousal disorder. Furthermore, all women were in stable, heterosexual, monogamous relationships for at least 1 year. Most studies included a dosing regimen of 100mg of flibanserin once daily at bedtime.

Overall, at least 7914 women were assigned to any treatment arm, of which 5914 women completed the various trials. An overview of study participant flow and number of dropouts per reason is presented in *Supplemental Table 2*.

General characteristics of the study participants

Five studies reported characteristics of the study participants (*Supplemental Table 3*). These characteristics did not differ between studies or treatment arms except for the mean (SD) age of 36.1 years (6.7) and 55.5 years (5.4) in premenopausal and postmenopausal women, respectively. Mean (SD) BMI was 26.9 (5.8), and nearly 90% of participants were of Caucasian descent. No information was found on level of education and socio-economic status. Study exclusion criteria specified an extensive list of diseases and medications.
Women's mean (SD) number of baseline SSEs per month was 2.5 (2.6) (*Supplemental Table 4*). Baseline e-Diary desire (scale 0-84) was 11.5 (9.3), and FSFI desire (scale 1.2-6) was 1.8 0.7).

Quality evaluation

Even though all studies were randomized controlled trials, the overall quality of the evidence for both efficacy and safety outcomes was very low (*Table 2*). The summary of the within-study risk of bias assessment can be found in *Supplemental Table 5, 6*, and *7A-7H*.

Table 1. General characteristics of the included randomized controlled trials[a].

Study	Trial number	Surveillance period	Country	N assigned / N completed per arm[b]	Menopausal status	Primary efficacy outcomes	Duration of FU
DeRogatis, 2012[24]	NCT00360529	2006-2008	USA and Canada	F 100mg: 290/199 F 50mg: 295/230 Placebo: 295/234	Pre	SSE and e-Diary desire	24 weeks
Thorp, 2012[28]	NCT00360555	2006-2008	USA and Canada	F 100mg: 396/251 F 50mg: 393/259[c] F 25mg: 396/274[c] Placebo: 399/287	Pre	SSE and e-Diary desire	24 weeks
Katz, 2013[26]	NCT00996164	2009-2011	USA	F 100mg: 543/408 Placebo: 547/446	Pre	SSE and FSFI desire	24 weeks
Simon, 2014[27]	NCT00996372	2009-2011	USA	F 100mg: 468/365 Placebo: 481/397	Post	SSE and FSFI desire	24 weeks
Alternate Dose Study	NCT00360243	2006-2008	USA	F 50mg: NR/336[c] F 50mg: NR/363 F 25mg: NR/337[c] Placebo: NR/349	Pre	SSE and e-Diary desire	24 weeks
EU Study	NCT00491829	2007-2009	Europe[d]	F 100mg: 316/202 F 50mg: 311/216 Placebo: 318/243	Pre	SSE	24 weeks
Terminated Study[e]	NCT01057901	2010-2011	USA and Canada	F 100mg: 376/116 Placebo: 372/124	Post	SSE and FSFI desire	24 weeks
Goldfischer, 2011[25]	NCT00277914	2006-2007	USA and Canada	F: 163/132[f] Placebo: 170/146	Pre	SSE and e-Diary desire	24/48 weeks[g]

[a] All analyses were performed by last observation carried forward; all studies were sponsored by Boehringer Ingelheim, who owned flibanserin at the time all studies were begun. Flibanserin was subsequently sold to Sprout Pharmaceuticals Inc and finally sold to Valeant Pharmaceuticals International Inc after US Food and Drug Administration approval.
[b] All dosages are once daily at bedtime unless otherwise stated.
[c] These dosages are twice daily.
[d] Participating European countries were Austria, Belgium, Czech Republic, Finland, France, Germany, Hungary, Italy, the Netherlands, Norway, Spain, Sweden, and United Kingdom.
[e] This study was terminated early by the study sponsor for commercial reasons, and has no published peer-reviewed study or abstract, but results are reported at clinicaltrials.gov. The premature study termination could have resulted in inadequate power for analysis of the individual study.
[f] Data were provided only for 3 flibanserin arms combined: 100mg once daily, 50mg twice daily, and 50mg once daily.
[g] 24 weeks of double-blind period was preceded by 24 weeks of open-label period.
BI=Boehringer Ingelheim, EU=European Union, F=flibanserin, FSFI=female sexual function index, FU=follow-up, LOCF=last observation carried forward, mg=milligram, N=number, NA=not applicable, NR=not reported, post=postmenopausal women, pre=premenopausal women, RCT=randomized double-blind placebo controlled trial, SSE=satisfying sexual event using e-Diary, USA=United States of America.

Table 2. Summary of the evidence quality grading using GRADE[a].

	Efficacy outcomes	**Safety outcomes**
Quality rating, before downgrading.	High. All studies were randomized controlled trials.	High. All studies were randomized controlled trials.
Within-study risk of bias	'Serious limitation'. The quality was downgraded because the risk of bias of the included studies was unclear or high (eTable 5, 6, and 7A-H). Of particular concern was the shift of primary endpoint from e-Diary desire to FSFI desire. Furthermore, dropout rates were high and it remained unclear how many responses were used to extrapolate the SSE to a 28-day period	'Serious limitation'. The quality was downgraded because the risk of bias of the included studies was unclear or high (eTable 5, 6, and 7A-H). Of particular was that the investigator defined drug-related and severe AEs were provided in only 2 studies and that dropout rates were high.
Indirectness evidence	'Serious limitation'. Women with a wide range of diseases and medication uses were excluded from study participation. Furthermore, women were on average overweight, and they might represent a higher functioning group given the base rate of 2.5 SSE's per month and their willingness to engage in sexual activity at least once per month. Finally, the dropout rate was higher in women taking flibanserin compared to placebo.	'Serious limitation'. Women with a wide range of diseases and medication uses were excluded from study participation. Furthermore, women were on average overweight, and they might represent a higher functioning group given the base rate of 2.5 SSE's per month and their willingness to engage in sexual activity at least once per month. Finally, the dropout rate was higher in women taking flibanserin compared to placebo.
Heterogeneity	'No limitation'.	'No limitation'. Moderate heterogeneity occurred for dizziness (I2 58.3%, p=0.035), which could be explained by menopausal status (I2 32.2%, p=0.219 in premenopausal women only). Substantial heterogeneity occurred for any AEs (I2 79.9%, p<0.001). Indeed, any AEs consisted of a very heterogenic group of side-effects, including the 4 most common AEs, but also events like upper respiratory tract infection, which could vary seasonally.
Imprecision	'No limitation'.	'Serious limitation'. Both in the individual studies and to a lesser extent in the overall effect size for particularly dizziness, somnolence, and AEs leading to study discontinuation, the confidence intervals are wide.

Table 2. Continued

	Efficacy outcomes	**Safety outcomes**
Publication bias	'Serious limitation'. 3 out of 8 studies were results from unpublished trials, of which the primary completion year ranged from 2008-2011.	'Serious limitation'. 3 out of 8 studies were results from unpublished trials, of which the primary completion year ranged from 2008-2011.
Final judgement	Very low quality	Very low quality

[a] The GRADE Working Group grades of evidence are as follows: (1) high quality, further research is very unlikely to change the group's confidence in the estimate of effect; (2) moderate quality, further research is likely to have an important impact on the group's confidence in the estimate of effect and may change the estimate; (3) low quality, further research is very likely to have an important impact on the group's confidence in the estimate of effect and is likely to change the estimate; (4) very low quality, the group is very uncertain about the estimate.
AEs=adverse events, FSFI=Female Sexual Function Index, GRADE=Grades of Recommendation, Assessment, Development, and Evaluation, SSE=satisfying sexual event.

Table 3. Overview of flibanserin[a] efficacy and safety outcomes.

	DeRogatis, 2012	Thorp, 2012	Katz, 2013	Simon, 2014	Alternate Dose Study[b]	EU Study	Terminated Study[c]	Goldfischer, 2011[d]
Efficacy outcomes, difference in mean (95% CI) changes from baseline for flibanserin compared to placebo[e]								
SSE	0.80 (0.20 to 1.40)	0.80 (0.09 to 1.51)	1.00 (0.44 to 1.56)	0.40 (0.12 to 0.68)	0.00 (-0.62 to 0.62)	0.60 (0.02 to 1.18)	0.30 (-0.17 to 0.77)	0.90 (0.08 to 1.72)
e-Diary desire	2.20 (-0.45 to 4.85)	1.70 (-0.51 to 3.91)	NA	NA	0.20 (-2.29 to 2.69)	2.30 (0.09 to 4.51)	NA	3.30 (0.24 to 6.36)
FSFI desire	0.40 (0.13 to 0.67)	0.30 (0.03 to 0.57)	0.30 (0.03 to 0.57)	0.30 (0.03 to 0.57)	0.20 (-0.07 to 0.47)	0.20 (-0.07 to 0.47)	0.20 (-0.07 to 0.47)	0.30 (0.03 to 0.57)
Safety outcomes, flibanserin/placebo, %								
Any AEs	66.6 / 59.3	69.4 / 58.8	62.2 / 50.5	63.4 / 51.7	NA	81.3 / 50.0	33.0 / 21.1	32.5 / 32.4
Investigator defined drug-related AEs	NR	NR	36.5 / 15.8	29.9 / 12.7	NR	NR	NR	NR
AEs leading to study discontinuation	11.4 / 3.4	15.7 / 10.8	9.6 / 3.7	8.1 / 3.5	NA	NR	NR	1.2 / 2.4
Dizziness	9.0 / 1.7	12.2 / 2.0	10.3 / 1.1	9.9 / 3.1	NA	14.6 / 4.4	6.4 / 3.5	0.6 / 2.9
Somnolence	11.0 / 3.1	11.9 / 3.5	14.4 / 3.5	8.8 / 1.5	NA	5.1 / 0.9	6.9 / 2.2	NR
Nausea	11.4 / 4.1	11.9 / 4.0	7.6 / 2.2	7.5 / 3.5	NA	12.3 / 6.0	5.3 / 4.1	1.2 / 3.5
Fatigue	6.2 / 2.7	9.6 / 6.8	5.7 / 3.3	NR	NA	17.1 / 10.4	NR	0.6 / 1.8
Severe AEs	NR	NR	4.2 / 3.5	6.0 / 3.5	NR	NR	NR	0.6 / 3.5
Serious AEs	1.0 / 0.0	NR	0.7 / 0.4	1.7 / 0.8	NA	6.0 / 5.0	1.6 / 1.1	0.6 / 0.6

[a] Unless otherwise indicated, flibanserin was administered in a single 100-mg dose at bedtime.
[b] This study used flibanserin, 50mg, twice daily.
[c] This study was terminated early by the study sponsor for commercial reasons, and has no published peer-reviewed study or abstract, but results are reported at clinicaltrials.gov. The premature study termination could have resulted in inadequate power for analysis of the individual study.
[d] This study started with a 24 week open-label period, after which only women who showed a predefined improvement were randomized to a 24 week double-blind period. Data were provided only for 3 flibanserin dosage arms combined: 100mg once daily, 50mg twice daily, and 50mg once daily.
[e] Scales of efficacy outcomes: SSE =number per 4 weeks; e-Diary desire = score per 4 weeks (scale 0-84); FSFI desire =score per 4 weeks (scale 1.2-6.0).
AEs=adverse events, CI=confidence interval, EU=European Union, F=flibanserin, FSFI=Female Sexual Function Index, mg=milligram, N=number, NA=not applicable (measure was not listed as predefined outcome), NR=not reported (measure was listed as predefined outcome=but not reported), P=placebo, SD=standard deviation, SSE=satisfying sexual event.

Beneficial treatment effects

An overview of reported efficacy and safety outcomes is presented in *Table 3*. For all efficacy outcomes, it was feasible to pool the results, except for Patient's Global Impression of Improvement (*Supplemental Table 8*).

Given the presence of mostly unclear risk of bias in the blinding domains, we sought to pool the results of the efficacy outcomes as described in the Methods section. Pooled efficacy analyses included all available studies, except Goldfischer, 2011, owing to its deviating 'withdrawal' study design. The Alternate Dose Study compared 50mg twice daily to placebo; all other included studies used the 100mg once daily at bedtime dosing regimen.

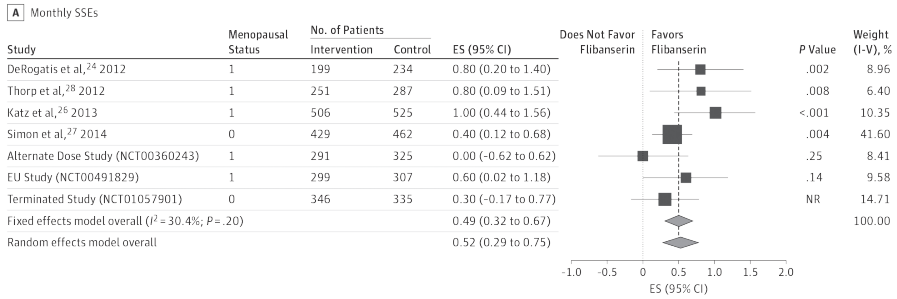
The pooled mean difference for change in mean SSE from baseline was 0.49 (95% CI, 0.32 to 0.67) between 100mg flibanserin and placebo (*Figure 1A*). In premenopausal women only, this was 0.65 (95% CI, 0.38 to 0.92) (*Supplemental Table 9*), and in studies using the FDA-approved 100mg once daily dose this was 0.54 (95% CI, 0.35 to 0.73) (*Supplemental Table 10*). For published studies, the mean difference for SSE was 0.58 (95% CI, 0.37 to 0.80) and for unpublished studies this was 0.31 (95% CI, 0.00 to 0.62)(*Supplemental Table 11*). The mean difference for e-Diary desire score mean change from baseline, which was only measured in studies with premenopausal women, was 1.63 (95% CI, 0.45 to 2.82) (*Figure 1B*). For FSFI desire, this was 0.27 (95% CI, 0.17 to 0.38) in all women (*Figure 1C*). All primary and secondary efficacy outcomes (*Supplemental Figure 2A-D*) showed a statistically significant difference between 100mg flibanserin vs placebo (p<0.001) in main analyses. An overview of the meta-analysis results for the efficacy outcomes in flibanserin and placebo groups separately can be found in *Supplemental Table 12*.

Harmful treatment effects

All except two safety outcomes were feasible to pool, and all studies assessed the effect of 100mg flibanserin once daily versus placebo. The risk for any AEs, which also included non-drug related side-effects such as common cold, was 1.29 (95% CI, 1.15 to 1.45) times higher for flibanserin than for placebo (*Supplemental Figure 3A*). Investigator-defined drug-related AEs were reported by 2 studies and ranged from 29.9 to 36.5% for flibanserin and from 12.7 to 15.8% for placebo. The risk for study discontinuation owing to AEs was 2.19 (95% CI, 1.50 to 3.20) times higher for flibanserin than for placebo, but this outcome was only reported in 4 studies (*Supplemental Figure 3B*).

The risk of dizziness was 4.00 (95% CI, 2.56 to 6.27) times higher with flibanserin than with placebo; for somnolence, 3.97 (95% CI, 3.01 to 5.24) times higher with flibanserin; for nausea, 2.35 (95% CI, 1.85 to 2.98) times higher with flibanserin; and for fatigue, 1.64 (95% CI, 1.27 to 2.13) times higher with flibanserin (*Figure 2*). The overall risk ratio for the 4 most common AEs was 2.86 (95% CI, 2.32 to 3.52). Severe AEs, defined as being incapacitating or causing inability to work or undertake activity, such as syncope, hypotension, injury, and severe manifestations of side-effects such as somnolence and dizziness, were reported

Figure 1. Mean differences in 3 measures of sexual desire, 100mg flibanserin vs placebo.

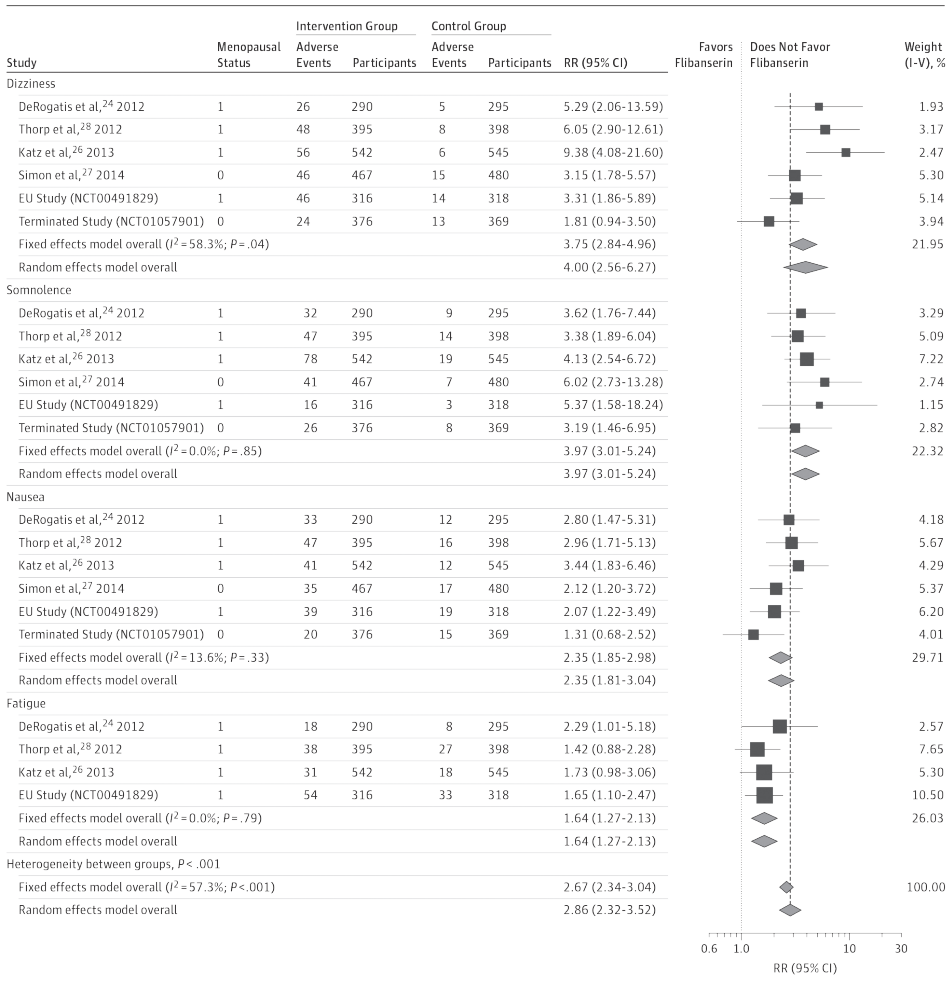


A: Monthly number of sexually satisfying events (SSEs). B: e-Diary desire (scale 0-84). C: Female Sexual Function Index (FSFI) desire (scale 1.2-6.0). Menopausal status: 1 indicates premenopause; 0 indicates postmenopause. CI=confidence interval, ES=effect size, I-V=inverse-variance, No=number, NR=not reported.

by 2 studies; in flibanserin users, the percentages were 4.2 and 6.0%, and 3.5% in controls. Serious AEs were defined as those resulting in death, those that were immediately life threatening, those that required longer lasting hospitalization, or those that were deemed serious for any other reason; these included, among others, appendicitis, cholelithiasis, and concussion.[29] The absolute number of serious AEs was small and the risk ratio did not differ between flibanserin and placebo users (1.48 (95%CI, 0.91 to 2.41)) (*Supplemental Figure 3C*). All safety outcomes, except serious AEs, showed a statistically significant difference between 100mg flibanserin vs placebo (p<0.001) in main analyses.

None of the studies was found to be too influential on the overall effect size when

Figure 2. Risk ratios (RRs) for the 4 most common adverse events, for 100mg flibanserin vs placebo.



Menopausal status: 1 indicates premenopause; 0 indicates postmenopause. CI=confidence interval, I-V=inverse-variance.

omitted 1 by 1. The direction, size, and significance of the associations remained the same in the sensitivity analyses performed based on the assumptions made regarding the imputation process detailed in the Methods section (*Supplemental Table 13*).

DISCUSSION

This systematic review and meta-analysis summarizes 5 published and 3 unpublished studies investigating efficacy and safety of flibanserin for the treatment of HSDD in nearly 6000 women. Treatment with flibanserin, on average, resulted in half of one additional satisfying sexual event per month, while substantially increasing the risk of dizziness, somnolence, nausea, and fatigue. Overall, the quality of the evidence was graded as very low for efficacy and safety outcomes, particularly due to limitations in design, indirectness of evidence, and more favorable efficacy outcomes in published compared to unpublished studies.

To our knowledge, this is the first systematic review and meta-analysis addressing the impact of flibanserin treatment in women with HSDD. The most important question concerns the clinical relevance of the statistically significant efficacy outcomes,[30] particularly considering side-effects that could worsen with concurrent alcohol intake or CYP3A4 inhibitors, including oral contraceptives and fluconazole.[7 31] Clinical significance was evaluated by assessing the magnitude of effect sizes, and by patient reported minimum relevant difference and self-perceived meaningful benefit.[30 32]

The data presented in this review suggest that the meaningful change caused by flibanserin is minimal. Firstly, for the range of 0.5-1.0 increase in SSEs reported by the FDA,[33] frequently referenced by scientific articles and mass media, the difference in SSEs change per month in our review was at the lower end of this range in main, subgroup, and sensitivity analyses (Supplemental Table 9-11, 13). Secondly, the perceived minimum important difference for the SSE e-Diary in postmenopausal women ranged from 0.16-1.84 per month.[34] Hence, the mean difference for change in SSE per month in this study was also at the lower end of this spectrum (Figure 1A). Patient Benefit Evaluation and Patient's Global Impression of Improvement measured overall subjectively experienced improvement. The difference in experienced meaningful benefit between flibanserin users and controls was small, ranging from 'minimal improvement' to 'no change' (Supplemental Table 8 and Supplemental Figure 2D).

The most common reported side-effects were of mild and moderate intensity, and serious side-effects were equally low in flibanserin and placebo users. This reflects positively on flibanserin's safety, but the conclusion that flibanserin is safe is premature. Investigator-defined drug-related AEs and severe AEs were underreported (2 studies each). Severe AEs included, among others, syncope and hypotension. Both can occur with flibanserin use alone but are amplified with concurrent alcohol use and were labelled by the FDA as serious safety concerns.[33] In an open-label extension study with a median follow-up time of 1 year, including 1.723 women, 723 (43%) reported investigator-defined drug-related AEs and 143 (8.3%) reported severe AEs.[35] The continued safety (and efficacy) of flibanserin with long-term use remains to be established.

The strengths and limitations of our work merit careful consideration. The systematic search for eligible studies in numerous medical databases, trial registries, and reference lists using broad search terms, and the inclusion of published and unpublished work, allowed us to provide a comprehensive overview of the evidence for the efficacy and safety of flibanserin for the treatment of women with HSDD. The inclusion of studies focusing on postmenopausal women took into account the potential off-label use. Furthermore, the extensive quality evaluation may facilitate the discussion of not only efficacy and safety of flibanserin, but also of reliability of the evidence put forward by the studies included in this review.

A limitation was the fact that the studies were light on details. This affected the accuracy of the quality evaluation (many within-study risk of bias domains remained with unclear risk) and the completeness of the meta-analyses (some outcomes were not feasible to meta-analyze and some meta-analyses did not include all studies). Therefore, some caution is required with interpreting the results of these assessments. The most important lacking data included blinding ascertainment, number in analyses, and completeness (effect and precision estimate) of every outcome. Contacting study investigators and study sponsor did not generate additional information. Therefore, given the unclear risk of bias for blinding, results were pooled via 2 different approaches, and yielded comparable findings, which generates confidence with regard to the reliability of the findings. Also, missing values were imputed to limit introduction of bias and proved robust in sensitivity analyses.

As women with a wide range of medication uses, diseases (including psychological comorbidities), and women not in a stable, communicative, heterosexual relationship were excluded from participation, the generalizability of the findings may be limited.[36] Because overall, study participants were overweight, results may not be generalizable to women in other BMI categories. Additionally, it is unclear to what extent they represent typical women HSDD, given that they had baseline 2.5 SSEs per month and had to be willing to engage in sexual activity once a month to be eligible to participate. Because the actual base rate of SSE's in women with HSDD is unknown, it is possible that the included women represent a higher functioning group, and conclusions may not be valid for all women suffering from HSDD.[22]

CONCLUSIONS

With nearly 90% of American physicians indicating that they would prescribe an approved HSDD pharmacological product over available non-pharmacological treatments[37], the need for sound evidence on the efficacy and safety profile of flibanserin is evident. The findings of this review suggest that the benefits of flibanserin treatment are marginal, particularly when taking into account the concurrent occurrence of side-effects. It has been suggested that women with HSDD would benefit most from an integrative approach, including, medical, psychiatric, psychological, couple relationship, and sociocultural domains: the biopsychosocial model.[11 17] Before flibanserin can be recommended in guidelines and clinical practice, future studies should include women from diverse populations, particularly women with (a history of) somatic and psychological comorbidities, medication use, and surgical menopause.

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Supplemental material

Supplemental material related to this article can be found online at *http://jamanetwork.com/journals/jamainternalmedicine/article-abstract/2497781*.

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CHAPTER 5

General discussion

The appreciation of a health-focused approach is increasingly gaining attention. This is reflected in the expanding number of contemporary definitions of health, which are available today. Within these definitions, different body systems could be considered subdomains of health, such as cardiovascular health or sexual health. The complex physiological mechanisms within these subdomains, which can interact with both psychological as well as social functioning, can differ between men and women and across stages of life.

To date, it remains to be elucidated how concepts of health apply to men and women, populations, and across stages of life and how health measurement should be operationalized. Therefore, the aim of this thesis was to study health and ageing in older adults from a gender-specific and life-course perspective. A better understanding of the patterns and determinants of health has the potential to aid women and men, professionals, and policy makers in their efforts towards obtaining, recovering, maintaining, and improving health in our ageing populations.

In this general discussion, the principal findings of this thesis will be summarized, after which the methodological considerations will be discussed. Thereafter, the findings and implications of this thesis will be reflected on from different perspectives, the population, clinical, and policy perspective. The discussion will be concluded with a section that reflects upon potential directions for future research.

PRINCIPAL FINDINGS

Economic impact of non-communicable diseases

In Chapter 2 we studied the economic impact of six non-communicable diseases (NCDs), including coronary heart disease, stroke, type 2 diabetes, cancer (lung, colon, cervical, and breast), chronic obstructive pulmonary disorder, and chronic kidney disease, at different levels of society, from the household to the governmental level. In a systematic review of 64 studies including more than 835 million individuals, NCDs imposed a large and growing global economic impact on households and impoverishment, in all continents and at all levels of income (**Chapter 2.1**). Financial catastrophe was often used as an outcome, and was defined as a scenario in which out-of-pocket expenditures for health care exceeded a certain percentage of the household income, varying from 10-40%. Financial catastrophe due to the selected NCDs occurred globally and ranged from 6-84% of the households depending on the chosen catastrophe threshold.

In total, 153 studies focused on the economic impact of NCDs at the macro-economic level, and suggested a steady global increase in healthcare expenditure over the years as well as excessive losses in national income, hampering economic development (**Chapter 2.2**). The costs varied across countries, regions, NCD type, severity of disease, and years lived with disease. In both Chapters 2.1 and 2.2, studies from low and middle income countries were underrepresented. Furthermore, heterogeneity in sample selection procedures, ascertainment of chronic disease, and in the definitions and measurement of the outcome (i.e. economic burden) made it difficult to draw definite conclusions. However, it is likely that the impact exerted by NCDs is underestimated, since important economic domains, such as coping strategies and inclusion of marginalized and vulnerable people who do not seek health care, are under highlighted in literature.

Healthy ageing and cardiovascular health

In **Chapter 3.1** we developed a comprehensive healthy ageing score in the population-based Rotterdam Study and explored age and gender differences in great detail. The healthy ageing score included 7 biopsychosocial domains: chronic diseases, mental health, cognitive function, physical function, pain, social support, and quality of life. Overall, we found that levels of healthy ageing score in this population were lower in women compared to men, in all age categories. Fewer women had multimorbidity (i.e. more than 1 chronic disease) compared to men. However, women had poorer mental health, worse physical function, more pain, and lower quality of life compared to men. The healthy ageing score declined with increasing age, albeit slightly steeper in women. Additionally, a higher healthy ageing score was strongly associated with lower mortality in both genders.

In **Chapter 3.2** we explored the association between healthy ageing score with markers of biological ageing, including with predicted transcriptomic age (PTA), predicted DNA methylation age (PDMA), and with leucocyte telomere length (TL). PTA was predicted with a leave-one-out-prediction meta-analysis, using whole-blood gene expression levels for half of the genes of the human genome. PDMA and TL were measured in the genomic DNA, which was extracted from peripheral venous blood. PDMA was calculated with a DNA methylation age calculator using penalized regression models. TL was measured using qPCR as the ratio of telomere repeat length to the copy number of the single-copy gene 36B4. Overall, we found that a higher healthy ageing score was associated with lower PTA and PDMA, and with longer TL in both genders, which could be mostly explained by chronological age.

Adopting a life-course approach in **Chapter 3.3**, we assessed whether established and previously unexplored characteristics of women's fertile life period and sex steroids were related to the healthy ageing score in postmenopausal women of the Rotterdam Study. We found that the healthy ageing score improved for women who had experienced menarche at an older age, were older at the time they went through menopause, had a longer fertile lifespan, or had more children, particularly living children, irrespective of socio-economic and lifestyle factors. Moreover, with increasing estradiol levels, healthy ageing score significantly worsened, whereas no associations were found for testosterone, free androgen index (FAI), and sex hormone-binding globulin (SHBG).

The counterintuitive direction of effect of estradiol in Chapter 3.2, was also found in **Chapter 3.4**. In this chapter, we were interested in the association between estradiol, testosterone, FAI, and SHBG with cardiovascular health in men and women of the

Rotterdam Study. The concept of cardiovascular health was introduced by the American Heart Association in 2010 and consists of 7 metrics including 3 health factors (total cholesterol, fasting glucose, and blood pressure) and 4 health behaviours (physical activity at goal, non-smoking, normal body mass index, and a healthy diet).[1] Ideal cardiovascular health has been associated with less severe subclinical atherosclerosis[2-4] lower incidence of cardiovascular morbidity and mortality,[4-8] better cognition[9], better psychological status[10], lower cancer risk [11], more favourable overall functional status [12], and lower all-cause mortality.[7 8] In our study, higher levels of SHBG were associated with better cardiovascular health in men. Among women, lower levels of testosterone and FAI and higher levels of SHBG were associated with better cardiovascular health. Furthermore, women with higher levels of estradiol tended to have worse cardiovascular health, although this effect attenuated after adjustment for covariates.

Women's sexual, reproductive, and menopausal health

We observed that although many studies focus on menopausal health or elements hereof in literature, such studies lack consensus of what menopausal health actually is. Therefore, we sought to conceptualize healthy menopause and aimed to incorporate biological as well as psychosocial aspects of health into the framework. We organized an expert panel meeting, inviting among others, gynaecologists, cardiologists, and epidemiologists, to develop a user-based conceptual framework for healthy menopause. We proposed healthy menopause as "a dynamic state, following the permanent loss of ovarian function, which is characterized by self-perceived satisfactory physical, psychological, and social functioning, incorporating disease and disability, allowing the attainment of a women's desired ability to adapt and capacity the self-manage". Such a multidimensional concept asks for multidimensional measurements. Therefore, in this chapter we provided an overview of measurement tools that could be used to measure menopausal health.

In **Chapter 4.2** we explored whether differences occurred in androgen levels between women with various forms of ovarian (dys)function and whether or not androgens in these women were associated with cardiometabolic features, such as blood pressure, glucose and cholesterol levels. Firstly, androgen levels were compared between 4 distinct groups of women: regular cycling women (i.e. healthy premenopausal women), women with polycystic ovary syndrome (PCOS, associated with hyperandrogenism), women with premature ovarian insufficiency (POI, associated with hypoandrogenism), and healthy postmenopausal women. As expected, women with PCOS were hyperandrogenic and women with POI were hypoandrogenic compared to regular cycling women. After adjusting for age, no differences were found between women with POI and healthy postmenopausal women and regular cycling and healthy postmenopausal women.
Secondly, the association between androgens with cardiometabolic features was assessed in these women. A higher FAI was associated with worse levels of cardiovascular risk factors in all groups of women, including elevated triglycerides, insulin,

homeostasis model assessment-insulin resistance (HOMA-IR), and blood pressure. These associations were strongest in women with PCOS. Although the strength of the associations attenuated after adjusting for body mass index (BMI), most associations in PCOS and healthy postmenopausal women remained statistically significant.

In **Chapter 4.3** we assessed the association between established and previously unexplored fertile lifespan characteristics, such as timing of childbirth and menopause, with all-cause and cause-specific mortality in postmenopausal women of the Rotterdam Study. We found that late first and last reproduction were protective for all-cause mortality, whereas a longer maternal lifespan (i.e. interval between birth of first and last child), post-maternal fertile lifespan (i.e. interval between birth of last child and age of menopause), and cumulative estrogen exposure were harmful for all-cause mortality. Moreover, the associations for late last reproduction, post-maternal fertile lifespan and cumulative estrogen exposure were strongest and most significant in 1-child mothers. In addition, the findings differed with regard to direction, size, and significant when stratifying the analyses for cardiovascular (CVD), cancer, and other mortality.

In August 2015, the US Food and Drug Administration (FDA) approved flibanserin as a medical treatment for women with hypoactive sexual desire disorder (HSDD). The approval of flibanserin at the intersection of science, policy, and advocacy received considerable attention in the public domain, and was accompanied by debates about the risk-benefit trade-off among stakeholders and health institutions. The systematic review and meta-analysis presented in **Chapter 4.4** summarized 5 published and 3 unpublished studies investigating the efficacy and safety of flibanserin for the treatment of HSDD in a little under 6000 women. Treatment with flibanserin resulted in one-half additional sexual satisfying event (SSE) per month while significantly increasing the risk of 4 common side-effects (dizziness, somnolence, nausea, and fatigue). Moreover, the quality of the studies was graded as very low, according to the applied Cochrane Grades of Recommendation, Assessment, Development and Evaluation (GRADE) Working Group approach.

METHODOLOGICAL CONSIDERATIONS

Systematic reviews, an exhaustive and reproducible approach

Three of the studies in this thesis were systematic reviews and meta-analyses. This study design is considered high quality evidence for several reasons. As opposed to narrative reviews, systematic reviews have a focused research question for which a specific search strategy is developed (*Table 1*), in our case by a medical information specialist. The design of a systematic review is reproducible and exhaustive. Reproducible in the sense that any other person should be able to reproduce the search and retrieve the same results. Exhaustive in the sense that all literature that fulfils the in- and exclusion criteria of

the research question is included. If literature is missing, authors of missing studies are asked to provide their study results and experts in the field are consulted to suggest any missing work. Moreover, grey literature can be searched for example via Google and trial registries can be consulted to retrieve unpublished results from intervention studies. The standardized approach for identification, selection, and appraisal of the studies allows scientists to synthesize all research objectively, without bias. We followed this approach for all three of the systematic reviews presented in this thesis.

Table 1. Comparison of main features between narrative and systematic reviews.[13]

Feature	Narrative review	Systematic review
Question	Broad in scope	Focused question
Sources and search	Not usually specified, potentially biased	Comprehensive sources and explicit search strategy
Selection	Not usually specified, potentially biased	Criterion-based selection, uniformly applied
Appraisal	Variable	Rigorous critical appraisal
Synthesis	Mostly a qualitative summary	Qualitative of quantitative summary
Inferences	Sometimes evidence-based	Usually evidence-based

The power of a prospective cohort design

Most of the studies in this thesis were performed in the Rotterdam Study, a prospective population-based cohort study.[14] A prospective cohort is a powerful study design to identify determinants of common health outcomes at the population level. One of the strengths of a prospective study design, such as the Rotterdam Study, is that information on determinants (i.e. sex steroids or fertile lifespan characteristics) can be collected before outcomes (i.e. cardiovascular health, healthy ageing score, or mortality) occur. This can reduce the extent of recall bias and it provides an opportunity to measure the temporality of a relation, in such that the determinant precedes the outcome. Another strength of the Rotterdam Study is that extensive information was available both for the exposures studied in this thesis as well as for the outcomes. This allowed us to study health and ageing from a gender-specific and life-course perspective in great detail.

Healthy, healthier, healthiest

The Rotterdam Study recruited individuals living in the well-defined Ommoord district of Rotterdam.[14] The overall response rate for inclusion at baseline was 72% (14.926 of 20.744 participants). Although these response rates are quite good, one could wonder how representative the participants of the Rotterdam Study are for the general

population. Population-based cohort studies tend to represent a more healthy and affluent population than the underlying general population eligible for inclusion in the study.[15] Rotterdam Study participants had a slightly lower cardiovascular risk compared to the total group of invitees, and nonparticipation was associated with mortality.[15] Therefore, in our studies, selective participation at baseline of healthier individuals could have resulted in more optimal levels of healthy ageing score (Chapter 3.1 and 3.2) and cardiovascular health (Chapter 3.3) among the included participants as compared to the general population. Hence, the findings may not be generalizable to less healthy populations.

Furthermore, selection bias can occur as a result of selective loss to follow-up, such as selective drop-out or selective inclusion. This could have occurred in our studies. For example, the healthy ageing score was constructed at the fourth visit of the first cohort, given that measurements of quality of life and social support were introduced at that time. Furthermore, we excluded participants who had missing data in more than 5 of the 7 healthy ageing score domains. It is likely that less healthy participants died before they were able to participate in our studies and that the less healthy had more missing data than the healthier participants, and were therefore more likely to have been excluded. In all of the studies we observed that the included population was younger, higher educated and suffered less from prevalent chronic disease compared to the total population at baseline, though the differences were minor. Although in our studies multiple procedures were used to reduce selective dropout of unhealthier participants to a minimum, selection bias due to this reason still might have remained.

Women are not small men

Too often in biomedical research, the effect of gender is not adequately considered, or not taken into account at all. This is also referred to as gender blindness.[16] Historically, women were excluded from study to prevent biases due to hormonal differences between men and women. Then, the findings from men were extrapolated back to women. At present, a prominent approach in biomedical research is to group men and women together, while adjusting the analyses for gender. A substantial pitfall of such an approach is that the effect of gender is considered a confounding effect, which is an effect that you want to get rid of.

The default of research analyses ought to be changed. Rather than adjusting for gender and analysing men and women together, by default research questions should be evaluated by gender. Reporting findings by gender has the potential to teach us more about the biological differences that occur naturally between men and women. Therefore, for all studies reported in this thesis, the analyses were performed in a gender-specific manner.

Measurement of women's fertile lifespan characteristics

Fertile lifespan characteristics, including age at menarche, menopause, and timing of childbirth, were assessed when women already reached menopause. Therefore,

retrospective recall could have occurred. One study assessed the validity of self-reported age at menarche in adulthood, and concluded that the correctness of the recall was moderate.[17] For age of menopause, such studies have shown that the recall is precise close to menopause, and starts to show more variance the larger the time since menopause interval is.[18] [19] In our population the measurement of fertile lifespan characteristics were collected before the assessment of the outcomes (such as mortality). Moreover, the women of the Rotterdam Study and interviewers administering the women's health questionnaire were unaware of the research questions under study. We therefore reasonably expect that any misclassification of the exposure would be non-differential, and if any, would provide a conservative approach given that the effect estimates would be less strong than if no misclassification would have occurred.

Natural postmenopausal women

By design, there is a risk of confounding in cohort studies. Confounding can be defined as 'the confusion of effects'.[20] Restricting the analyses to a particular subgroup of the population is an example of a way to control for confounding during the study design stage of a study. In our studies including women, analyses were restricted to postmenopausal women with a natural menopause. This was done because health status' can differ greatly between pre, peri and postmenopausal women, given that the menopausal transition is characterized by significant changes at the hormonal, physiological, and metabolic level.[21] [22] To what extent these changes affect later life health further differs according to menopausal type (i.e. natural vs. surgical menopause). Furthermore, in the analyses where sex steroids were the exposure of interest, the population was further restricted to women who never used estrogenic hormone replacement therapy. These restrictions were applied to reduce the amount of bias in our effect estimates, since menopausal status, menopausal type, and hormone replacement therapy are considered factors that are associated with both the exposures and the outcomes under study in this thesis.

Adjustment for confounders

A second way to deal with confounding is by adjusting the analyses for factors that are associated with both the exposure and the outcome under study. In this thesis, these factors included socio-economic status (e.g. level of education, income, marital status) and lifestyle variables (e.g. smoking, body composition, alcohol, physical activity, diet). For women, the variable years since menopause was additionally included, which was defined as the interval between a woman's age of menopause and her actual age. Women of the same age can have different ages of menopause. Given that timing of menopause is associated with sex steroid levels, fertile lifespan characteristics and postmenopausal health, years since menopause was included as a covariate in the statistical models. Although we did our best to rule out as much confounding as possible via complementary approaches, residual confounding can never be completely ruled out in cohort studies.

FINDINGS IN PERSPECTIVE

An extensive discussion of the findings for each separate chapter can be found in the discussion sections of the separate manuscripts included in this thesis. In this general discussion, we will reflect on the findings and implications of our work from different perspectives: the population, the clinical, and the policy perspective.

Population perspective

Financial hardship

In most studies of this thesis, we incorporated the population's perspective. This perspective could be described as the way people perceive a situation through their own eyes. High proportions (up to 90%) of individuals and households perceived changes for the worse and worried about their financial situation (e.g. financial hardship) due to the impact of non-communicable diseases in their families. Economic consequences of non-communicable diseases are preceded by self-perceived illness and treatment seeking behaviour, according to a theoretical framework presented by McIntyre and colleagues.[23] People may avoid seeking health care when ill, ignore being ill, or not perceive themselves as being ill altogether.[23] These factors together could have led to an underestimation of the true economic burden that NCDs impose on households and on the impoverishment of people. In order to constrain this burden, country and even region specific financial protection should be put into place. Significantly fewer households would become impoverished when out-of-pocket spending is reduced to less than 15% of total health spending.[24] Other promising approaches include subsidized or free hospital services and the provision of certain health services to the poor.[24]

Disability paradox

Considering self-perceived health is essential for both men and women and for all age groups. This is particularly true in the elderly for whom subjectively experienced health can differ substantially from what is measured objectively.[25] This is referred to as the disability paradox: individuals suffering from disease or disability often concurrently report high levels of quality of life.[26] [27] In this thesis we observed this trend: of the people with multimorbidity (i.e. suffering from more than 1 chronic disease), 43% reported moderate and 45% reported good quality of life. Of people with severe disability, these percentages were 49% and 15%, respectively. These numbers were similar in men and women. Notably, the thresholds used for good and moderate quality of life in this population were stringent, because most of the participants reported high levels of quality of life. Hence, when studying health in older populations, combining measures of self-perceived health with more objective measures may better reflect the health status of individuals.

Consequences of complete

Ideal cardiovascular health was defined by de American Heart Association as having ideal levels of 3 health factors (such as blood pressure < 120/80 mmHg) and 4 health behaviors (such as BMI < 25 kg/m^2).[1] The cutoffs for ideal levels originated from established guidelines and were literature-based.[1] In Chapter 3.3 we found that none of the participants adhered to the definition of ideal cardiovascular health, a finding that has been found consistently in other populations.[4-8] Should the conclusion therefore be that our entire populations are unhealthy, at least from a cardiovascular point of view? Or are the thresholds to define ideal cardiovascular health too stringent? Although the first may be true, one could reason in favor of the second. The approach used to define ideal cardiovascular health shows some similarity with the definition of health from the World Health Organization (WHO) from 1948: "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity".[28] The definition has been criticized, since complete implies that most of us would be unhealthy for most of the time.[29] Although complete well-being is a desirable goal, it is hard to achieve and challenging to operationalize. When criteria for health are set at too stringent levels, the study of its determinants and consequences is hampered.

Satisfactory and dynamic health

Living with chronic disease and disability is becoming more and more common. This is a second reason why the previously mentioned WHO definition has become outdated: its static nature makes an increasing number of people definitely ill.[30] In a recent paper published by a group of international health experts, health is defined as 'the ability to adapt and the capacity to self-manage', herein moving from a static definition toward a more dynamic formulation of health.[30] In the conceptual framework for healthy menopause, we took the dynamicity of health as a starting point, and further incorporated a people perspective by emphasizing self-perceived satisfactory functioning and a woman's desired ability to adapt and capacity to self-manage, hereby allowing women to gain more control over their health. By doing so, we anticipated on the previously described disability paradox: disease and disability do not necessarily affect an individual's sense of well-being or quality of life. Disease, disability and health can coexist at different degrees, changing dynamically over time, differing between men and women and within the same individual across different stages of life.

Clinical perspective

Healthy vs successful ageing. A semantic discussion?

Ageing in an optimal manner is described with many different words, two of which are the terms healthy ageing and successful ageing. Are they two terms for the same thing, or do they reflect distinct phenotypes? The term successful ageing seems to be predominantly popular in American settings, whereas healthy ageing is more commonly

used in European settings. To date, many different definitions of healthy or successful ageing exist, and many frameworks have been proposed by groups across the globe.[31-37] To some extent the frameworks show overlap, but they also include distinct features depending on the region or context in which they are developed. Concerns have been raised as to the term 'successful', which may stretch beyond the semantic preference of the users.[38] Successful ageing could be problematic in the sense that it suggests inappropriate ideas of failure and unattainable ideals for success.[38] It ignores the fact that decline is inevitable while ageing and it places the responsibility to delay decline primordially on the individual. However, most environmental challenges that people encounter during life, lie outside of their reach. In our developed healthy ageing score, we accommodated objective measures of health as well as measures of self-perceived health and created a continuum-based score, ranging from 0-14. A continuum-based score makes it easier to detect changes in healthy ageing over time, compared to the more conventional successful vs non-successful ageing approach.

Sex steroids & sex differences

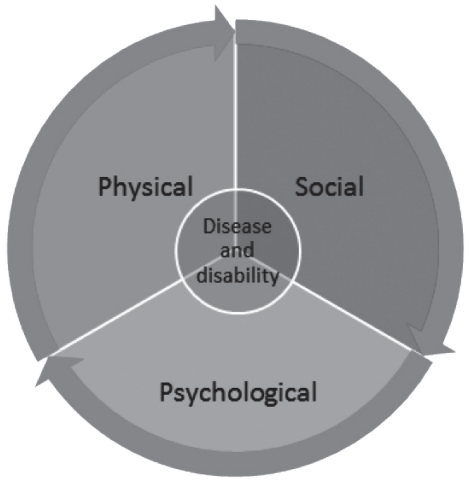
The more testosterone, the better it is for men. The more estradiol, the better it is for women. These are two expressions that still resonate in science and practice today. The pivotal role of sex steroids in bodily systems, such as the cardiovascular system, makes them a promising interventional target. This has led to the roll-out of intervention studies, such as the Women's Health Initiative, which hypothesized that estrogenic hormone replacement therapy in women would lower cardiovascular disease risk.[39] Yet, both testosterone treatment in men and estrogenic hormone replacement therapy in women have not lived up to their expectations thus far, at least with regard to benefits for the cardiovascular system.[40-43] In this thesis, we found that higher levels of testosterone did not remain significantly associated with better cardiovascular health after adjustment for confounders in men. Higher testosterone and FAI were associated with worse cardiovascular health and cardiovascular risk factors in both pre- and postmenopausal women. Moreover, higher levels of estradiol were associated with worse cardiovascular health in postmenopausal women, a counterintuitive finding. The same direction of effect was also found for the association between estradiol with healthy ageing score. In line with our findings, an increasing number of studies is finding the same unfavourable effect of higher levels of estradiol in women.[44-52] These findings imply that the effects of sex steroids in bodily systems are complex and differ between men and women. More research is needed to confirm our findings and identify specific mechanisms behind these findings. Several potential explanations have been discussed in the separate chapters of this thesis, particularly Chapters 3.2 and 3.3.

Biopsychosocial model

One of the pillars of clinical practice is the biopsychosocial model. This model systematically considers biological, psychological, and social factors and their interactions to understand health and disease (*Figure 1*). [53] Practical issues, such as lack of time or budget, could

have led to different disciplines, including medical doctors, psychologists, and social workers emphasizing one specific domain of the model more than the others. The biopsychosocial model provided the basis for the studies on healthy ageing and healthy menopause in this thesis. The multidimensional healthy ageing score consisted of, among others, measures of physical functioning, cognitive functioning, mental health, and self-perceived social support. While conceptualizing healthy menopause, the complementary relation between physical, psychological, and social functioning shaped the framework. These papers may be useful for clinical practice, in the sense that they could facilitate the implementation of sustainable biopsychosocial healthcare in clinical, public health, and research settings and aid health care workers to monitor healthy ageing of their patients over time. In fact, the public health department of the municipality of Utrecht is exploring whether they can implement the healthy ageing score, or an adapted version hereof, in the periodic health measurements that they perform among their community-dwelling older adults.

Figure 1. The biopsychosocial model, incorporating disease and disability.



Sexual desire: spontaneous or contextual?

The biopsychosocial model may also provide some explanation for the low efficacy of flibanserin found for women with HSDD, among other reasons. Eminently, sexology is a field of wherein biological, psychological, and social domains go hand in hand. Let's assume for a moment that the suggested physiological mechanism of action for flibanserin is sound, and that this drug can restore the balance between excitatory and inhibitory activity of the brain by reducing levels of serotonin and increasing levels of dopamine and norepinephrine.[54] This mechanism of action is founded on the (abandoned)

conception that sexual desire occurs spontaneously from an internal sexual drive.[55] Research suggests that the nature of sexual desire and arousal are conditioned upon an arousable system and the presence of sexually rewarding stimuli in an appropriate context: the incentive motivation model.[56 57] Hence, it could have been expected that solely treating women with HSDD with flibanserin would yield little or no effect, because this approach is too unidimensional. Women with HSDD may benefit most from approaches integrating medical, psychological, couple-relationship, and sociocultural domains.[58 59] Reasonably, this also applies to patients with divergent health problems, hereby further emphasizing the importance of biopsychosocial thinking in clinical care, research, and public health settings.

Windows of opportunity in women's life

The importance of a life-course approach in women's health has only recently been adopted in guidelines for women's health,[60 61] but studies are still scarce. There is growing support that functioning, disease, and health in older adults share common pathways with accumulative life experiences, which can start as early as in utero.[33 62] The work presented in this thesis is novel in such that we assessed how female-specific life course determinants impacted later life health both independently and cumulatively. We found that different measures of reproductive performance, such as pregnancy, reproductive disorders, and timing of menopause, were related to later life health. Therefore, reproductive performance in women could be considered an important marker of general health and health in later life. The identification of women with deviating reproductive performance earlier in life could facilitate the development of adequate preventive strategies to keep this women healthy until old age.

To implement such strategies, several windows of opportunity in women are available. The average age of menarche in our population was 13 years. The average age at first birth was 25 years, and the average age of menopause was 50 years. These natural life stages are specific to women and can affect women's lives beyond the ovaries and reproductive performance. Moreover, the time window that occurs when transitioning from one life phase to another, for instance the onset of puberty, the maternal period or the menopausal transition, provides a unique opportunity for education, evaluation of signs and symptoms, promotion of healthy lifestyle, personalized counseling, and recognition and potential treatment of modifiable risk factors.

Policy perspective

Population strategies for health

In Chapter 2 of this thesis, we showed that NCDs have an impact at the microeconomic as well as the macroeconomic level. Three factors precede catastrophic health expenditure of households and encompass the availability of health services requiring payment, a low capacity to pay, and the presence of risk pooling mechanisms. Therefore, reducing

the microeconomic impact of NCDs on households requires a macroeconomic health systems approach that is not reliant on out-of-pocket payments for treatment and provides financial risk protection.[24] Although investing manpower and money into curative health care is essential, there is another promising side to the same medal: public health. Illustratively, Statistics Netherlands recently released a report in which they stated that cancer mortality among men reduced by 30% in the past 30 years.[63] A large part of this decrease was attributable to the reduction in lung cancer mortality. Although advances in medical treatment claimed a 10-20% share, the largest reduction was due to anti-smoking regulatory mechanisms and smoking cessation campaigns.[64]
Population strategies to facilitate a healthier lifestyle have several important advantages in the sense that they radically attempt to diminish the underlying causes of disease, they can benefit entire populations, and they are behaviourally appropriate.[65] The latter is illustrated in the non-smoking example. When non-smoking becomes the social norm, for instance because it is prohibited in public places, it results in adapted non-smoking behavioural habits among the population.
However, population strategies are plagued by the Prevention Paradox.[65] How large the benefits of a healthy lifestyle are at the population level, how small they tend to be at the individual level, particularly when it comes to short term successes. Lifestyle measures are not only important to prevent disease, but even more so to maintain and facilitate health. Ageing healthily enhances the lives of individuals. Moreover, it has social and economic implications in ageing populations and can relieve the pressure on public spending. This is an important insight that is increasingly recognized and anticipated on by policy makers around the globe.[66,67]

From binary to continuum-based health approaches

The tendency in our societies is to think about health and disease in a binary fashion, in such that an individual could be either healthy or diseased. This way of dealing with health and disease may not reflect its true nature, although dichotomization may be necessary for practical reasons.[68] Decades ago, the British medical doctor George Pickering described this phenomenon as follows: "the sharp distinction between health and disease is a medical artefact for which nature, if consulted, provides no support. This is difficult for doctors to understand, because this is a departure from binary thought. Medicine can count up to two, not beyond."
Binary thinking is also found in definitions and operationalizations of healthy ageing, or successful ageing. Rowe and Kahn described successful ageing as the absence of disease and disability, high cognitive and physical functioning, and active engagement with life. If you have all, then you are a successful ager.[34,35] In line with George Pickerings' proposed way of thinking, it has been suggested that more lenient and continuum-based measures for healthy ageing may better capture the heterogeneity of the phenotype.[69,70] This approach was adopted whilst developing the healthy ageing score in this thesis. Moreover, we incorporated disease and disability into the conceptual framework of healthy menopause. Moving from a binary health vs. disease towards a more integrated way of thinking, where even the diseased could be healthy to some extent, may aid health professionals and policy makers in facilitating the dynamic balance between every day opportunities and challenges in ageing populations.

Evaluating research questions by gender

In this thesis, we found gender differences in healthy ageing score and for the association between sex steroids with cardiovascular health. Moreover, women specific factors affected healthy ageing and mortality. However, by default, women and men are combined in the analyses and reporting of research findings. In clinical practice, symptoms reported by women are mostly considered atypical to those in men, instead of different. Furthermore, earlier life experiences, such as reproductive performance and pregnancy-related disorders, are often not adequately considered in later life health. Although there is still a long way to go, examples of good practice, that incorporate a gender-specific and life-course approach do exist. One such example is the Alliance of Gender and Health in the Netherlands, a collaboration between researchers, clinicians, and policy makers that emphasizes a gender-specific approach in research, training of doctors and psychologists, and awareness of the general public.[71] Also, the first guideline on cardiovascular risk management after reproductive and pregnancy-related disorders in the Netherlands is now a fact.[60] At the European level, most, but not all, EU grant applications include the following question: "Where relevant, describe how sex and/or gender analysis is taken into account in the project's content".[72] These examples are a good start, although more of such measures and efforts are needed at the national and international level, to sustain a gender-specific and life-course approach.

Science and politics: a daring affair?

In August 2015, flibanserin was approved by the US Food and Drug Administration (FDA) for the treatment of women with HSDD. The approval of flibanserin at the intersection of science, advocacy, and policy was controversial, of which I would like to provide a short history in this general discussion.[73] In 2009, flibanserin was submitted to the FDA for approval for the first time. The committee unanimously voted against, given that the observed side-effects did not outweigh the still unclear benefits. They expressed the need for a third trial, with less restrictive inclusion criteria, and for studies focusing on the interaction between flibanserin, drugs, and alcohol. In 2013, the drug was resubmitted for approval, now including this third trial, though the inclusion criteria were still stringent. An alcohol interaction study was performed in 25 people, of which 23 were men. The study showed that concurrent intake of flibanserin with small amounts of alcohol substantially increased the risk of hypotension and fainting. Therefore, the FDA rejected approval once more. Then, in 2015, flibanserin was resubmitted for the final time and it got approved. The risk/benefit ratio was still the same. So if the science didn't change, what did? In the meanwhile, the pharmaceutical company that owned flibanserin helped launch an advocacy platform called 'Even the Score', which framed a strong promotional campaign directed at all levels of society.[74] Also, the FDA got accused of sexism, because

medications approved for men's sexual dysfunction are many whereas women have none. From this example can be taken that politics, advocacy and science interact closely, and that it can be difficult to disentangle to what extent different factors influence decision-making processes.

DIRECTIONS FOR FUTURE RESEARCH

In this thesis we started out studying the economic impact of NCDs. Thereafter, we looked at gender differences in cardiovascular health and in the newly developed healthy ageing score. Furthermore, we assessed whether women's fertile lifespan characteristics and sex steroids influenced postmenopausal health. Based on the findings and methodological considerations of our work, several potential directions for future research can be highlighted. As a starting point, future research should consider studying men and women in a gender-specific manner and adopting a life-course approach.

Economic impact of NCDs

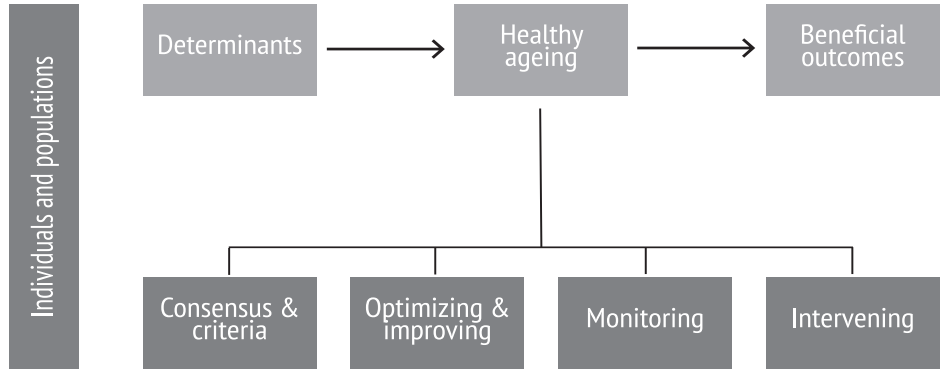
For all studies in this thesis where men and women were involved, we stratified the analyses by gender from the start. Although we anticipated to do the same for the economic impact reviews, this was infeasible given that the individual studies mostly reported their findings for men and women together. Future studies focusing on the economic impact of NCDs should consider studying the impact by gender. Furthermore, there is a need for cost-effectiveness studies that can show which strategies are promising to reduce the economic impact of NCDs in different contexts. These studies should consider including the less studied indirect financial burden of NCDs on households, such as lost earnings, cost of premature death, and educational dropout among children. Besides focusing on the effect of strategies on long term outcomes (such as reductions in national health care spending), such studies would benefit from the additional inclusion of short term outcomes (such as coverage and adherence to interventions) in order to adequately inform politicians and decision makers.

Healthy ageing research

Consensus & criteria

Measurement of healthy ageing is still in its infancy, although more and more research groups are working on operationalizing it in their populations. Therefore, several directions for future research could be suggested (*Figure 2*). The healthy ageing field could benefit greatly from establishing international consensus as to how healthy ageing should be measured and which gold standard measures could be acceptable to represent the underlying construct that is being measured. Moreover, there is a need for explicit and testable criteria for the development of healthy ageing measurement tools. A good example of such an approach was published by Searle and colleagues for the development of frailty indeces.[75] Frailty is defined as the accumulation of deficits. Criteria for the inclusion of deficits were, among others, that the deficit should be associated with the health status, that it should be associated with age (p-value < 0.1), that the deficit does not saturate too early, and that it should be measured in at least 70% of the participants. Reaching consensus on such criteria for healthy ageing measurement tools will make judgment of the quality of the tools easier and will facilitate better comparisons of healthy ageing between different populations across the globe.

Figure 2. Graphical representation of potential directions for future healthy ageing research. Healthy ageing could be studied at the individual and population level. Furthermore, research could focus on determinants and potential beneficial outcomes related to healthy ageing, and on the four topics mentioned at the bottom of the figure.



Optimizing and improving healthy ageing measurement

It is possible that certain healthy ageing domains are more important than others. Furthermore, how healthy ageing should be measured can differ between men and women, in different age groups, and between populations (such as between countries or ethnic groups). For example, cultural beliefs and attitudes towards health and differences in social networks may require different approaches to healthy ageing measurement. In the development of the healthy ageing score in this thesis we deliberately chose to give all domains the same weight to make the score easy to interpret and more feasible to apply in other populations. The relative importance of certain healthy ageing domains could be assessed by creating a multivariable prediction rule. However, before such an approach can be implemented, outcomes that can serve as adequate gold standard measures for healthy ageing need to be established via the consensus mentioned above. New gender-

specific or country-specific health markers and measures could be added to such models in order to assess how healthy ageing measurement tools could be improved.

Monitoring and intervening on healthy ageing

Measuring and monitoring healthy ageing could allow for a better understanding of patterns and trajectories of healthy ageing, how healthy ageing changes over time, and how it differs between individuals and populations at different levels of society. Moreover, there is a paucity of research that focuses on determinants of healthy ageing. Determinants that are of particular interest include, among others, lifestyle factors, gender-specific factors, and environmental factors. Furthermore, it remains unclear which interventions are effective with regard to obtaining, maintaining and improving healthy ageing. Therefore, a potential direction for future research includes the assessment of interventions which could be beneficial for different (sub)-groups of the population. Intervention studies could be implemented at the individual or population level. An example of an intervention directed at maintaining healthy ageing at the individual level could be to educate women in perimenopause about the physiology of menopause and the symptoms and symptom relief options of menopausal symptoms at the general practitioner's office. An example of an intervention at the population level to improve healthy ageing could be to study the effect of taxing products containing sugar or fat and increasing the availability of more inexpensive healthy food choices. Finally, cost-benefit studies could provide a valuable insight as to which interventions are the most promising to invest in with regard to enhancing the lives of individuals and populations.

Women's health research

From in utero to postmenopause

We studied the impact of women's fertile lifespan characteristics on mortality and healthy ageing. We were able to go back to the timing of menarche, but did not have information on early childhood or in utero exposures, both of which have been suggested to affect later life health.[33 62] Moreover, we might have not measured characteristics of the fertile life that may affect the health status of older women. Such characteristics could include pregnancy complications, stillbirths, and abortions. It was outside the scope of this thesis to study the effect of earlier life experiences specific to men in more detail. It needs no further explanation that such studies could provide valuable insights for men's later life health. Furthermore, the women included in our studies were mostly postmenopausal and we were not able to compare women across stages of menopause in detail. It would be of interest to repeat some of our work in populations where women can be stratified for menopausal stage, in order to assess the timeliness and durability of the associations under study.

Paradigm shift

Reproductive success and delayed ovarian ageing, which could be measured with proxies as late age of menopause, late last reproduction and number of living children, could be viewed as early markers of women's general health in later life.[76-80] Reproductive success and delayed ovarian ageing are linked to longevity via common genetic factors related to DNA repair and maintenance, and immune and mitochondrial function.[77 80 81] Therefore, it could be that the occurrence of menopause is a consequence of the ageing of the soma that results from the deterioration of these functions. In our studies we found a protective effect of late menopause and more living children on healthy ageing in postmenopausal women, though no association was found for late last reproduction. The age of last reproduction was not extreme enough in our population. Therefore, more studies are needed assessing the impact of these early life markers on health in later life in contemporary populations with more extreme ages of birth. Moreover, genetic studies are needed to further explore the genetic link between reproductive success, longevity, and health.

CONCLUSIONS

In our modern societies, where we have the prospect of living over 100, it is becoming increasingly meaningful to study health and ageing from an integrated, gender-specific, and life-course perspective. This is true for men, and even more so for women, who tend to spend have of their life in postmenopause. Although the appreciation of a health-focused approach is increasingly gaining attention, it remains under highlighted how concepts of health apply to men and women, populations, and across stages of life and how health measurement should be operationalized.

In this thesis we conceptualized, developed, and reflected on different definitions of health and subdomains of health, and applied these definitions to the population-based Rotterdam Study. All research questions involving men and women were stratified by gender, and considerable differences between men and women were observed and discussed. Moreover, we specifically focused on women's sexual, reproductive and menopausal health, and found that female factors such as pregnancy and timing of menopause impacted women's later life health.

A better understanding of gender-specific and life-course determinants of health has the potential of promoting and sustaining health in men and women. Moreover, improvements in measuring and monitoring health can contribute to a better aligning of health systems with the needs of ageing populations and could facilitate the development of age-friendly environments.

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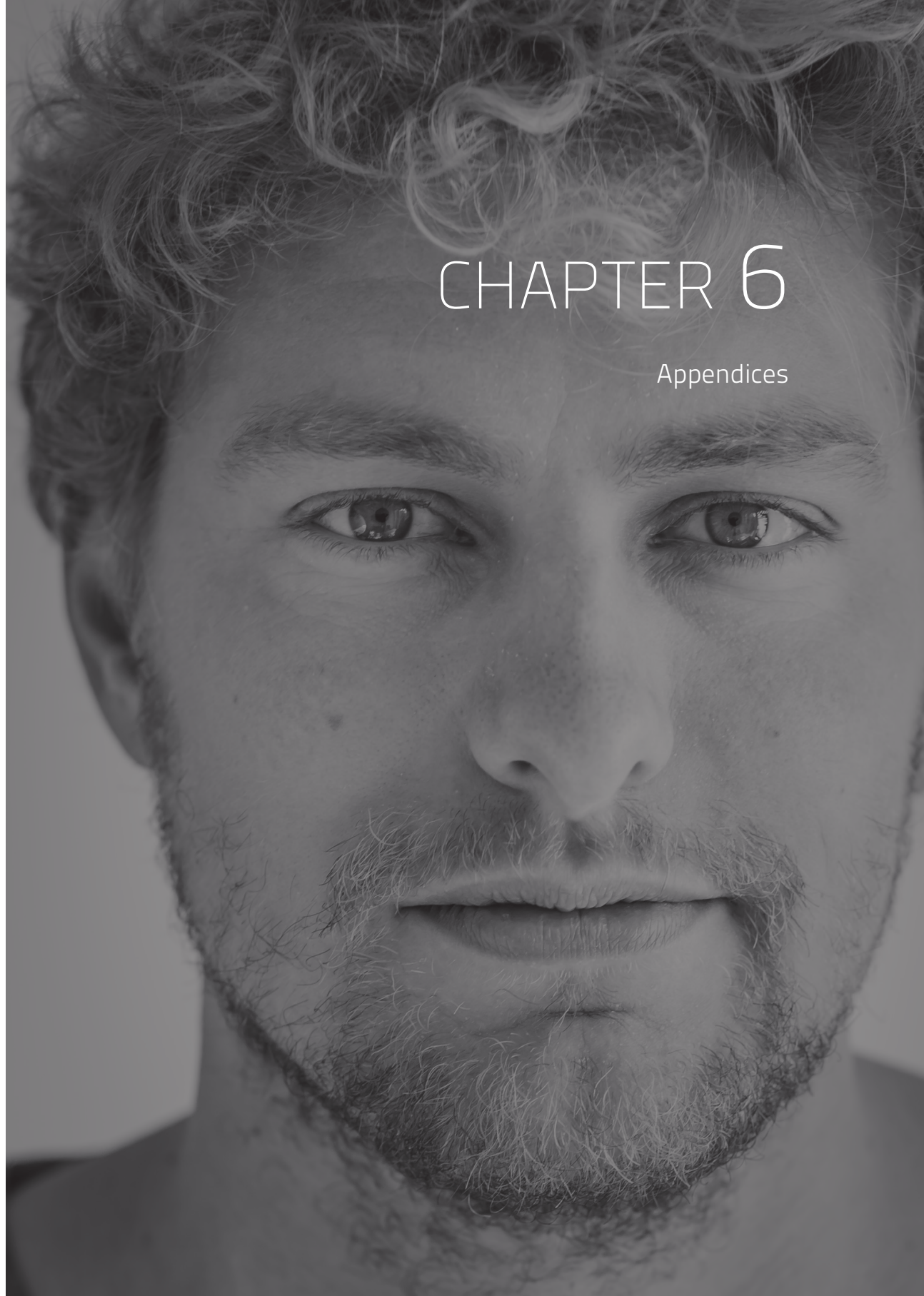
CHAPTER 6

Appendices



Summary

Our population is ageing. While people are living longer in all parts of the world, evidence suggests that these years are spent with more disease and disability. This is observed in both men and women, although gender differences do occur. Worldwide, men are outlived by women by 6 to 8 years. However, women generally spend these additional years in less health: 'men die quicker, women get sicker'. Furthermore, it has been shown that life events specific to women, such as pregnancy and timing of menopause, can greatly affect women's health later in life.
To date, past and current health research mostly focuses on individual risk factors, diseases, and mortality, and only marginally focuses on health. This approach may limit our overall understanding of health and the factors that are associated with obtaining, maintaining, and improving health. A better understanding of ageing healthily has the potential to enhance the lives of individuals and can facilitate the development of adequate strategies with regard to the economic and social implications of ageing populations. The benefits of a health-focused approach extend beyond the individual, and can impact all levels of society, ranging from the household to the governmental level.

In this thesis we aimed to provide insights in health and ageing of older adults whilst adopting an integrated, gender-specific, and life-course approach. As a first step we studied the global micro-economi¬¬c and macro-economic impact of NCDs in societies. Thereafter, we developed a healthy ageing score and applied the new concept of cardiovascular health to the population-based Rotterdam Study, after which we assessed age and gender differences and the role of sex steroids. Furthermore, because women encounter experiences throughout their lives that are exclusive to them, in this thesis we specifically focused on conceptualizing healthy menopause and on the role of fertile lifespan characteristics and different types of ovarian dysfunction in cardiometabolic and overall health.

In **Chapter 2** of this thesis, we studied the economic impact of non-communicable diseases (NCDs) on households, impoverishment, health care spending, and national income. This was done by performing 2 systematic reviews. The NCDs included were coronary heart disease, stroke, cancer, type 2 diabetes mellitus, chronic obstructive pulmonary disorder, and chronic kidney disease.
The first systematic review is presented in **Chapter 2.1**, and focused on the economic impact of NCDs on households and impoverishment. We identified 64 articles that fulfilled the pre-specified inclusion criteria, which included more than 835 million individuals. The findings of this study showed that NCDs imposed a large and growing impact on households and impoverishment, in all continents and at all levels of income.
In **Chapter 2.2**, we took a macro-economic approach, and observed a steady global increase in health care expenditure as well as excessive losses in national income due to NCDs.

For both systematic reviews, we found little to no data for the regions Africa, South-America, and the Middle-East. Also, most studies did not separate men and women in the presentation of their results. Therefore, in Chapters 2.1 and 2.2 we suggested that more research is needed particularly in these continents while presenting the results for men and women separately.

Considering the ageing of our population, healthy ageing is a priority public health challenge of growing importance. Therefore, in **Chapter 3.1** we developed a healthy ageing score in the population-based Rotterdam Study, assessed age and gender differences, and evaluated the association of healthy ageing score with mortality. In the Rotterdam Study, comprehensive and detailed information on subjective and objective measures, which are necessary to construct a healthy ageing score, are available. The Rotterdam Study is a prospective, population-based cohort of individuals aged 45 years and older who reside in the well-defined suburb of Ommoord in the city of Rotterdam, the Netherlands. The healthy ageing score included a total of 7 biological, psychological, and social domains, most of which were easy and inexpensive to measure with questionnaires. Overall, we found that levels of healthy ageing score in this population were lower in women compared to men, in all age categories. Fewer women had multimorbidity compared to men. However, women had poorer mental health, worse physical function, more pain, and lower quality of life compared to men. The healthy ageing score declined with increasing age, albeit slightly steeper in women. Additionally, a higher healthy ageing score was strongly associated with lower mortality in both genders.
In **Chapter 3.2** we explored the association between healthy ageing score with markers of biological
ageing, including with predicted transcriptomic age (PTA), predicted DNA methylation age (PDMA), and with leucocyte telomere length (TL). Overall, we found that a higher healthy ageing score was associated with lower PTA and PDMA, and with longer TL in both genders, which could be mostly explained by chronological age.
In **Chapter 3.3** we studied the association between women's fertile lifespan characteristics and sex steroids with the healthy ageing score in the Rotterdam Study. We found that women with a later menarche, a later menopause, a longer fertile lifespan, and women with more children, particularly living children, had more favourable healthy ageing score levels. These findings remained significant after adjustment for various socio-economic and lifestyle factors. Moreover, with increasing estradiol levels, healthy ageing score significantly worsened, whereas no associations were found for testosterone, free androgen index, and sex hormone binding globulin.
In **Chapter 3.4** we studied the association between sex steroids and sex hormone binding globulin with cardiovascular health in men and women of the Rotterdam Study. The concept of cardiovascular health was introduced by the American Heart Association in 2010 to facilitate both clinical and public health programs for concurrent health promotion and disease prevention. Cardiovascular health includes ideal levels of 7 metrics, 3 of which are health factors (total cholesterol, fasting glucose, and blood pressure) and 4 of which

are health behaviours (physical activity at goal, non-smoking, normal body mass index, and a healthy diet). In our study, sex steroids, and particularly SHBG, were associated with cardiovascular health in both men and women.

In **Chapter 4** we focused more specifically on women's sexual, reproductive, and menopausal health.
In **Chapter 4.1** we present the results of an expert meeting that we commenced to conceptualize healthy menopause. We proposed health menopause as "a dynamic state, following the permanent loss of ovarian function, which is characterized by self-perceived satisfactory physical, psychological, and social functioning, incorporating disease and disability, allowing the attainment of a women's desired ability to adapt and capacity the self-manage". Adopting such a unifying conceptual framework could facilitate the improvement of adequate preventative and treatment strategies, guide scientific efforts, and aid education and communication to health professionals and the public with regard to women's health in and around the menopausal transition and at different postmenopausal stages.
In **Chapter 4.2** we studied androgens and cardiometabolic factors (e.g. blood pressure, cholesterol levels, glucose, and more) in 4 distinct groups of women: regular cycling women (e.g. healthy premenopausal women), women with polycystic ovary syndrome (PCOS, associated with hyperandrogenism), women with premature ovarian insufficiency (POI, associated with hypoandrogenism), and healthy postmenopausal women. Hyperandrogenism is characterized by an excess of androgens (such as testosterone) whereas hypoandrogenism denotes a lack of androgens in the body. Both states have been associated with a higher risk of cardiovascular disease. We found that increased levels of androgens were associated with a worse cardiometabolic profile in all 4 groups of women. These associations were strongest in women with PCOS. This study suggests that androgens could be important factors in women's cardiometabolic health.
In **Chapter 4.3** we found that certain characteristics of women's fertile lifespan were associated with all-cause mortality and that the findings differed when stratifying the analyses for cardiovascular, cancer, and other mortality. More specifically we found that late first and last reproduction were protective for all-cause mortality, whereas a longer maternal lifespan (e.g. interval between birth of first and last child), post-maternal fertile lifespan (e.g. interval between birth of last child and age of menopause), and cumulative estrogen exposure were harmful for all-cause mortality. Interestingly, the findings were merely evident in 1-child mothers, whereas no associations were found in mothers with more children. This study emphasizes the importance of fertility characteristics for longevity, and underscores the need of taking into account different aspects of the fertile life with regard to women's later life health.
The final study presented in this thesis (**Chapter 4.4**) is a systematic review and meta-analysis of the efficacy and safety of flibanserin as a medical treatment for women with hypoactive sexual desire disorder. In total, 5 published and 3 unpublished studies including nearly 6.000 women fulfilled the inclusion criteria. The inclusion of published

and unpublished studies allowed us to capture a complete overview of the benefits and risks of flibanserin, without bias. We found that treatment with flibanserin resulted in one-half additional sexual satisfying event per month while significantly increasing the risk of 4 common side-effects (dizziness, somnolence, nausea, and fatigue). Additionally, we found that the quality of the evidence was very low.

Lastly, **Chapter 5** provides a general discussion of the work presented in this thesis. The principal findings were summarized, after which we discussed the main methodological considerations. Thereafter, the findings and implications of this thesis were reflected on from different perspectives, the population, clinical, and policy perspective. The general discussion was concluded with a section that delineates several potential directions for future research.

Samenvatting

Achtergrond en doel van dit proefschrift

Het aandeel van ouderen in de bevolking stijgt, een fenomeen dat ook wel vergrijzing wordt genoemd. Mensen worden heden ten dage steeds ouder. Dit is een trend die wereldwijd te zien is en onder andere verklaard kan worden door toegenomen welvaart, betere hygiënische voorzieningen en verbeteringen in de gezondheidszorg. De extra levensjaren worden niet per definitie in goede gezondheid doorgebracht. Integendeel, veroudering gaat vaak gepaard gaat met meer ziektes en beperkingen in het dagelijks functioneren. Dit geldt voor mannen, maar nog meer voor vrouwen. Ook al leven vrouwen gemiddeld genomen 6 tot 8 jaar langer dan mannen, doorgaans worden deze extra jaren in een slechtere gezondheid doorgebracht. In het Engels wordt dit uitgedrukt met het gezegde 'men die quicker, women get sicker'. Voorts zijn er factoren waar vrouwen gedurende hun leven mee te maken krijgen die specifiek voor hen zijn. Hierbij valt bijvoorbeeld te denken aan zwangerschap en de menopauze. Deze gebeurtenissen kunnen zelfs op oudere leeftijd de gezondheid van vrouwen blijven beïnvloeden.

Gezondheidsonderzoek focust zich doorgaans op losse risicofactoren (zoals roken of hoge bloeddruk) en op ziekten en mortaliteit. In feite focust slechts een klein gedeelte van gezondheidsonderzoek zich op het daadwerkelijke gezondheidsaspect. Deze benadering beperkt het begrip dat wij hebben van gezonde veroudering en de factoren die gepaard gaan met het verwerven, behouden en verbeteren van onze gezondheid. Het verleggen van de focus van een ziekte-gecentreerde naar een gezondheids-gecentreerde benadering sluit beter aan bij onze verouderende populatie, waarin het lijden aan chronische ziekten of beperkingen eerder regel dan uitzondering is. Zonder meer reiken de voordelen van een gezondheidsbenadering verder dan het bevorderen van gezondheid van het individu. Zo kan een gezondheidsbenadering een positief effect hebben op verschillende niveaus in de samenleving, variërend van het huishouden tot het bestuurlijke niveau.

Het doel van dit proefschrift is om vanuit een geïntegreerde, genderspecifieke levensloopbenadering inzicht te verkrijgen in gezondheid en veroudering van mannen en vrouwen van middelbare en oudere leeftijd. De meeste studies die beschreven staan in dit proefschrift, zijn onderdeel van de Rotterdam Studie. Dit is een groot bevolkingsonderzoek onder 15.000 mensen van 45 jaar en ouder uit de Rotterdamse wijk Ommoord. De overige studies die beschreven staan in dit proefschrift, zijn systematische literatuuronderzoeken.

Als eerste stap is getracht door middel van systematisch literatuuronderzoek vast te stellen wat wereldwijd de micro- en macro-economische impact is van chronische ziekten in de maatschappij. Daarna werd een instrument ontwikkeld om gezonde veroudering in

de Rotterdam Studie te meten. Daarbij is specifiek gekeken naar verschillen in gezonde veroudering tussen mannen en vrouwen in verschillende leeftijdsgroepen. Ook is het door de Amerikaanse hartstichting ontwikkelde concept van cardiovasculaire gezondheid toegepast op de deelnemers van de Rotterdam Studie. Specifiek is gekeken naar het verband tussen geslachtshormonen, waaronder oestrogenen en testosteron, met cardiovasculaire gezondheid. In het slothoofdstuk is de aandacht specifiek gericht op de gezondheid van vrouwen. Zo is er een definitie voor gezonde menopauze ontwikkeld en is het belang van vrouwspecifieke kenmerken van de reproductieve levensfase, zoals zwangerschap en timing van de menopauze, voor gezondheid bij vrouwen op latere leeftijd in kaart gebracht.

Bevindingen per hoofdstuk

In **hoofdstuk 1** wordt de achtergrond van dit proefschrift beschreven. **Hoofdstuk 2** beschrijft de economische impact van chronische ziekten op huishoudens, op armoede, gezondheidsuitgaven en inkomen op nationaal niveau. Hiervoor werden 2 systematische literatuuronderzoeken gedaan. Als chronische ziekten werden hart- en vaatziekten, kanker, diabetes mellitus (suikerziekte), chronisch obstructief longlijden en chronisch nierfalen gekozen.
Het eerste literatuuronderzoek staat in **hoofdstuk 2.1** en had als focus de economische impact op het niveau van huishoudens en armoede. In totaal voldeden 64 studies aan de inclusiecriteria die vooraf gesteld waren. Deze studies bevatten gezamenlijk meer dan 835 miljoen mensen. De conclusie uit het literatuuronderzoek was dat chronische ziekten in toenemende mate een belasting vormen voor de financiële situatie van huishoudens en dat wereldwijd steeds meer huishoudens in armoede geraken door de korte en lange termijn gevolgen van deze ziekten.
In **hoofdstuk 2.2** werd ten aanzien van de macro-economische impact van chronische ziekten een geleidelijke en wereldwijde stijging in uitgaven aan de gezondheidszorg en grote verliezen op het gebied van nationaal inkomen geobserveerd. Voorts bleek uit beide literatuuronderzoeken dat de economische impact van chronische ziekten in de gebieden Afrika, Zuid-Amerika en het Midden-Oosten sterk onderbelicht is en dat maar weinig studies de impact voor mannen en vrouwen apart bekeken. Op basis van deze bevindingen deden wij de aanbeveling dat toekomstig onderzoek zich specifiek op deze regio's zou moeten richten en daarin onderscheid zou moeten maken tussen de impact die chronische ziekten op mannen en vrouwen afzonderlijk kunnen hebben.

Hoofdstuk 3.1 gaat over de ontwikkeling van een maat om gezonde veroudering bij individuen en populaties te meten. Daarbij werd gekeken naar verschillen in leeftijd en geslacht en werd onderzoek gedaan naar de relatie tussen gezonde veroudering en mortaliteit. In de Rotterdam Studie was gedetailleerde informatie beschikbaar, die nodig was om een dergelijk meetinstrument te ontwikkelen. In totaal bevatte de maat voor gezonde veroudering 7 verschillende biopsychosociale domeinen, die allemaal

gemakkelijk te meten waren met behulp van vragenlijsten. Mannen hadden optimalere gezonde verouderingsscores dan vrouwen. Dit was het geval in alle leeftijdsgroepen (65-69 jaar, 70-74 jaar, 75-79 jaar, 80-84 jaar, en ≥85 jaar). Mannen hadden vaker dan vrouwen meer dan één chronische ziekte. Echter, vrouwen hadden in vergelijking met mannen een slechtere geestelijke gezondheid, een slechter fysiek functioneren, meer pijn en een lagere kwaliteit van leven. Mannen en vrouwen lieten beiden een daling in de gezonde verouderingsscore zien bij het ouder worden en deze daling was sterker bij vrouwen. Tot slot was bij mannen en vrouwen gezonde veroudering gerelateerd aan een lager risico op overlijden.

Hoofdstuk 3.2 gaat over de relatie tussen de gezonde verouderingsscore en verschillende markers van biologische veroudering. Biologische veroudering werd gemeten met een aantal afgeleiden van het genetische profiel van mensen. De gezonde verouderingsscore bleek sterk geassocieerd te zijn met deze markers van biologische veroudering in mannen en vrouwen, maar een groot deel van het effect werd verklaard door leeftijd.

Hoofdstuk 3.3 beschrijft de studie van het verband tussen vrouwspecifieke kenmerken van de reproductieve levensfase, geslachtshormonen (zoals estradiol en androgenen) en gezonde veroudering in postmenopauzale vrouwen van de Rotterdam Studie. Hieruit bleek dat vrouwen met een latere eerste menstruatie, een latere menopauze, een langere reproductieve levensperiode (leeftijd van menopauze minus leeftijd van menarche) en vrouwen met meer kinderen, betere gezonde verouderingsscores hadden. Ook hadden vrouwen met hogere estradiolwaarden, lagere en dus minder optimale gezonde verouderingsscores. Er werd geen verband gevonden met androgenen.

Hoofdstuk 3.4 gaat over het verband tussen estradiol, testosteron, de vrije androgeen index en het geslachtshormoon bindende eiwit SHBG met het door de Amerikaanse hartstichting ontwikkelde concept van cardiovasculaire gezondheid. Cardiovasculaire gezondheid werd door hen in 2010 gedefinieerd als het gelijktijdig hebben van normale waarden voor cholesterol, bloeddruk en glucose alsmede het hebben van optimaal gezond gedrag (niet roken, voldoende bewegen, gezond eten en geen overgewicht). In deze studie werd gevonden dat vooral SHBG gerelateerd was aan cardiovasculaire gezondheid bij zowel mannen als vrouwen.

In **hoofdstuk 4** ligt de focus specifieker op de seksuele, reproductieve en menopauze gezondheid van vrouwen.

Hoofdstuk 4.1 beschrijft de uitkomsten van een expertmeeting die werd georganiseerd om het concept van gezonde menopauze vorm te geven. In de expertmeeting werd vastgesteld dat de gezonde menopauze een dynamische staat van zijn is waarbij de ervaren tevredenheid ten aanzien van het biopsychosociale functioneren van de vrouw centraal moet staan.

Hoofdstuk 4.2 beschrijft de studie van androgenen en cardiometabole factoren (zoals bloeddruk, cholesterol en glucosewaarden) in vier groepen vrouwen: vrouwen met een regelmatige menstruatiecyclus (gezonde premenopauzale vrouwen), vrouwen met het polycysteus ovarium syndroom (PCOS, een hyperandrogene staat), vrouwen

met premature ovariële insufficiëntie (POI, een hypoandrogene staat) en gezonde postmenopauzale vrouwen. In de literatuur wordt zowel hyperandrogenisme (teveel androgenen) als hypoandrogenisme (te weinig androgenen) in verband gebracht met een verhoogd risico op hart- en vaatziekten. Uit deze studie kwam in alle vier de groepen vrouwen naar voren dat hogere androgeenwaarden verband hielden met een slechter cardiometabool profiel. De verbanden waren het sterkst voor vrouwen met PCOS. Deze bevindingen impliceren dat androgenen met betrekking tot het ontwikkelen van hart- en vaatziekten een rol kunnen spelen.

In **hoofdstuk 4.3** staat beschreven dat vrouwspecifieke kenmerken van de reproductieve levensfase gerelateerd zijn aan mortaliteit en dat de bevindingen veranderen wanneer de doodsoorzaken onderverdeeld worden in drie groepen (cardiovasculair, oncologisch en overige mortaliteit). Bijzonder was dat vrouwen die hun eerste of hun laatste kind op oudere leeftijd kregen een lager risico op overlijden hadden. Verder bleek ook dat vrouwen met een langer interval tussen het eerst en laatstgeboren kind, vrouwen met een langer interval tussen laatstgeboren kind en de start van de menopauze en vrouwen met een hogere blootstelling aan oestrogenen gedurende het leven een hoger risico hadden op overlijden. Deze studie onderstreept het belang om rekening te houden met eerdere levensfasen t.a.v. gezondheid bij vrouwen op latere leeftijd.

De laatste studie van dit proefschrift (**hoofdstuk 4.4**) is een systematische review en meta-analyse naar de effectiviteit en veiligheid van flibanserin als medicamenteuze behandeling voor vrouwen met verminderd seksueel verlangen. In totaal werden 5 gepubliceerde en 3 ongepubliceerde studies met in totaal bijna 6.000 vrouwen geïncludeerd. Het meenemen van zowel gepubliceerd als ongepubliceerd werk stelden ons in de gelegenheid om een compleet overzicht van de gunstige effecten en bijwerkingen van flibanserin te verkrijgen. Eén van de uitkomsten was dat flibanserin-gebruiksters een half keer per maand vaker seksuele activiteit rapporteerden waar ze tevreden over waren dan placebo-gebruiksters. Het risico op bijwerkingen was hoger in de flibanserin groep. De meest voorkomende bijwerkingen waren duizeligheid, slaperigheid (somnolentie), misselijkheid en moeheid. Voorts bleek dat de kwaliteit van de onderzochte studies laag was.

Tot slot staat in **hoofdstuk 5** de beschouwing van de bevindingen van dit proefschrift. Als eerste staat er een samenvatting van alle bevindingen, waarna de belangrijkste methodologische overwegingen worden bediscussieerd. Daarna volgt een reflectie op de bevindingen en implicaties vanuit 3 verschillende perspectieven: het populatie perspectief, de klinische praktijk, en het beleidsmatige perspectief. Het hoofdstuk wordt afgesloten met aanbevelingen voor toekomstig onderzoek.

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List of publications and manuscripts

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*these authors should be considered similar in author order.

PhD portfolio

Summary of PhD training and teaching activities

PhD student:	Loes Jaspers
Erasmus MC department:	Epidemiology
Research school:	Netherlands Institute of Health Sciences (NIHES)
PhD period:	August 2013 – February 2017
Promotors:	Prof.dr. O.H. Franco and prof.dr. J.S.E. Laven
Copromotor:	Dr. M. Kavousi

TRAINING

	YEAR	ECTS
Master of Science in Health Sciences, Clinical Epidemiology (NIHES)		
Core program		
Study Design	2013	4.3
Biostatistical Methods I: Basic Principles	2013	5.7
Methodologic Topics in Epidemiologic Research	2013	1.4
Clinical Epidemiology	2013	5.7
Biostatistical Methods II: Classical Regression Models	2013	4.3
Advanced short courses		
Women's health course	2014	0.9
Advanced analysis of prognosis studies	2014	0.9
Repeated measurements in clinical studies	2014	1.4
Quality of life measurement	2014	0.9
Psychology in medicine	2015	1.4
Erasmus Summer Programme		
Principles of research in medicine	2013	0.7
Clinical decision analysis	2013	0.7
Methods of public health research	2013	0.7
Health economics	2013	0.7
Markers and prognostic research	2013	0.7
The practice of epidemiologic analysis	2013	0.7
Causal inference	2014	0.7
Logistic regression	2014	1.4
Causal mediation analysis	2014	0.7

Joint models for longitudinal and survival data	2015	0.7
Methods of health services research	2015	0.7
General academic skills courses		
How to use Endnote, Medical Library, Erasmus MC	2014	0.3
Systematic literature retrieval, Medical Library, Erasmus MC	2014	0.6
Basic Course on R, Molecular Medicine, Erasmus MC	2014	1.4
Integrity in scientific research, Erasmus MC	2015	0.3
Attended seminars and workshops		
Seminars at the department of Epidemiology	2013-2016	1.0
ErasmusAGE research meetings	2013-2016	1.0
Cardiovascular epidemiology group research meetings	2013-2016	1.0
2020 Epidemiology research meetings	2013-2016	1.0
Workshop systematic reviews and meta-analyses, Erasmus MC	2014	0.3
Women's health course, Erasmus MC	2015	0.9
(Inter)national conferences and presentations		
Jaarsymposium Vereniging voor Vasculaire Geneeskunde, Hart- en vaatziekten bij vrouwen		
Attendance	2013	0.3
14th World Congress Menopause, Cancun, Mexico		
Attendance	2014	1.0
Rotterdam Science Festival		
Oral presentation	2015	0.3
10th European Congress on Menopause and Andropause, Madrid, Spain		
Poster presentation	2015	1.0
63rd meeting Society of Reproductive Investigation, Montreal, Canada		
Poster presentation	2016	1.0
Dutch Epidemiology Conference (WEON), Wageningen, the Netherlands		
Oral presentation	2016	0.3
9th World Congress on Active Ageing, Melbourne, Australia		
Oral presentation	2016	1.0
Other		
Organization of an expert meeting to conceptualize healthy menopause, Erasmus MC	2014	1.0
Peer review of articles for scientific journals:		

Maturitas, Vaccine, and the European Journal of Epidemiology	2014-2016	0.5
Board member and coordinator science working group, Dutch scientific Society of Sexology	2015-2016	2.0
Member of the guideline committee for management of the menopause, Dutch Menopause Society / Dutch Society of Obstetrics and Gynaecology	2015-2016	2.0
Student member of assessment panel epidemiology training programs, Dutch Society of Epidemiology	2016	0.5

TEACHING

	YEAR	ECTS
Lectures		
Lectures for the course Public Health in Low and Middle Income Countries, NIHES	2013-2015	0.5
Lecture for the medical sexology working group	2015	0.2
Lecture for the course Sexology, Faculty of Social Sciences, Leiden University	2016	0.2
Supervising of students' thesis work		
Lucía Gabriela Jaramillo Jácome, MSc thesis Clinical Epidemiology, NIHES		
Assistance with supervision	2016	0.3

Word of thanks

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About the author

Loes Jaspers was born on May 24th 1987 in Venray, the Netherlands. She spent the first part of her childhood in Sudan, Indonesia, and Zimbabwe, with her parents and brother Wouter. After moving back to the Netherlands, she graduated from secondary school (athenaeum) at Sint Stanislascollege, Delft, in 2005.

Subsequently, she started her medical education at Leiden University. During this period, she was a member of the international federation of medical students' associations (IFMSA) in the Netherlands, among others, as president of the local board in Leiden. Furthermore, she was involved in the implementation of a health education program in South Sudan with Mpower Foundation. She spent half a year in Indonesia for a research internship on human papillomavirus vaccination acceptance among parents. For this study, she was awarded a young investigator's prize by the International Gynaecologic Cancer Society in 2010. In 2012, she obtained her medical doctor's degree cum laude.

Loes started her PhD in 2013, at the department of Epidemiology of the Erasmus MC in Rotterdam, under the supervision of dr. Maryam Kavousi, prof.dr. Oscar Franco, and prof. dr. Joop Laven. The results of this work are presented in this dissertation. During her training period, she completed a postgraduate Master of Science in Clinical Epidemiology. In the same period, she finalized the theoretical part of the training program to become a sexologist, and took position as a board member of the Dutch Scientific Society of Sexology. In 2016, Loes was awarded the Lambers prize by the Erasmus University.

Loes will continue her work as a resident in infectious diseases control at GGD regio Utrecht, after which she is planning to train as a consultant in public health.