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**RISK FACTORS FOR PROSTATE CANCER:
ANALYSIS OF PRIMARY DATA, POOLING,
AND RELATED METHODOLOGICAL ASPECTS**

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RISK FACTORS FOR PROSTATE CANCER: ANALYSIS OF PRIMARY DATA, POOLING, AND RELATED METHODOLOGICAL ASPECTS

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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“Nothing in this book is true.”
—Kurt Vonnegut, *Cat’s Cradle*

Abstract

Prostate cancer is the second most common cancer among men worldwide, yet its etiology remains poorly understood. Obesity, on the other hand, is a prevalent but preventable medical condition that is associated with hormonal and metabolic changes. Since prostate cancer is a hormone-related cancer, the hypothesis of a link between body fatness and prostate cancer risk has been formulated. Furthermore, the considerable biologic heterogeneity of prostate cancer warrants analyses to be carried out separately by aggressiveness of the disease, differentiating indolent from potentially lethal tumors.

This thesis has two aims. First, to elucidate the association between obesity, as measured by body mass index (BMI), and the risk of localized, advanced, and fatal prostate cancer. This is done using both primary data (Paper I) and aggregated data extracted from published epidemiological studies (Paper IV). Second, to deal with some methodological aspects related to the analysis of primary and aggregated data (Paper II; Paper III; Paper V).

In Paper I, we used primary data from the Cohort of Swedish Men to examine the association of BMI during early adulthood (30 years of age) and middle-late adulthood (45–79 years of age) with the incidence of localized and advanced prostate cancer and with prostate cancer mortality. BMI during middle-late adulthood was observed to be inversely associated with the incidence of localized prostate cancer, while it was directly associated with the incidence of advanced prostate cancer and with prostate cancer mortality. At the same time, we observed limited evidence of an inverse association between BMI during early-adulthood and the risk of advanced and fatal prostate cancer.

In Paper II, we extended the use of quantile regression for censored data to those situations where the time scale of interest is attained age at the event instead of follow-up time. In particular, we described how to use Laplace regression to model percentiles of age at the event in the presence of delayed entries, by conditioning on age at entry.

In Paper III, we identified three major misinterpretations of risk and rate advancement periods (RAP): first, equating RAP with the difference in mean survival times; second, interpreting RAP as the time by which the survival curve for the exposed individuals is shifted compared with that for the unexposed; third, equating the RAP to a simple ratio of two log–relative risks. Furthermore, we showed how RAP estimation is sensitive to the specification of the age–disease association.

In Paper IV, we carried out a dose–response meta-analysis to summarize the available evidence on the association between BMI during middle-late adulthood and the incidence of localized and advanced prostate cancer. Based on aggregated data extracted from 13 prospective studies, we observed that BMI was inversely associated with the incidence of localized prostate cancer, while it was directly associated with the incidence of advanced prostate cancer.

In Paper V, we stressed the importance of assessing the goodness of fit of dose–response meta-analysis models. We presented and discussed three tools (deviance, coefficient of determination, and decorrelated-residuals–versus–exposure plot) that are useful to test, quantify, and visually display the fit of dose–response meta-analysis models, while taking into account the correlation structure of the study-specific log–relative risks.

In conclusion, Paper I and Paper IV supported the hypothesis of etiological heterogeneity of prostate cancer in relation to obesity during middle-late adulthood. In particular, BMI was observed to be directly associated with advanced prostate cancer and with prostate cancer mortality. Paper II extended the use of quantile regression for censored data to those situations where attained age is the time scale of interest, Paper III clarified the appropriate use and interpretation of RAP, and Paper V proposed useful and relevant methods for assessing the goodness of fit of dose–response models in research synthesis.

List of publications

- I. Andrea Discacciati, Nicola Orsini, Swen-Olof Andersson, Ove Andrén, Jan-Erik Johansson, and Alicja Wolk
Body mass index in early and middle-late adulthood and risk of localized, advanced and fatal prostate cancer: a population-based prospective study
British Journal of Cancer 2011; 105(7):1061–1068
- II. Andrea Bellavia, Andrea Discacciati, Matteo Bottai, Alicja Wolk, and Nicola Orsini
Using Laplace regression to model and predict percentiles of age at death, when age is the primary time scale
American Journal of Epidemiology 2015; 182(3):271–277
- III. Andrea Discacciati, Andrea Bellavia, Nicola Orsini, and Sander Greenland
On the interpretation of risk and rate advancement periods
International Journal of Epidemiology 2015; in press
- IV. Andrea Discacciati, Nicola Orsini, and Alicja Wolk
Body mass index and risk of localized and advanced prostate cancer—a dose–response meta-analysis of prospective studies
Annals of Oncology 2012; 23(7):1665–1671
- V. Andrea Discacciati, Alessio Crippa, and Nicola Orsini
Goodness of fit tools for dose–response meta-analysis of binary outcomes
Research Synthesis Methods 2015; in press

The articles will be referred to in the text by their Roman numerals, and are reproduced in full at the end of the thesis.

Related publications

- Andrea Discacciati, Nicola Orsini, Swen-Olof Andersson, Ove Andréén, Jan-Erik Johansson, Christos S. Mantzoros, and Alicja Wolk
Coffee consumption and risk of localized, advanced and fatal prostate cancer: a population-based prospective study
Annals of Oncology 2013; 24(7):1912–1918
- Andrea Discacciati, Nicola Orsini, and Alicja Wolk
Coffee consumption and risk of nonaggressive, aggressive and fatal prostate cancer—a dose–response meta-analysis
Annals of Oncology 2014; 25(3):584–591
- Andrea Discacciati and Nicola Orsini
Re: Coffee consumption and risk of prostate cancer: an up-to-date meta-analysis
European Journal of Clinical Nutrition 2014; 68(3):409–410
- Andrea Discacciati and Alicja Wolk
Lifestyle and dietary factors in prostate cancer prevention
Recent Results in Cancer Research 2014; 202:27–37
- Andrea Bellavia, Matteo Bottai, Andrea Discacciati, and Nicola Orsini
Adjusted survival curves with multivariable Laplace regression
Epidemiology 2015; 26(2):e17–e18
- Andrea Discacciati, Nicola Orsini, and Sander Greenland
Approximate Bayesian logistic regression via penalized likelihood by data augmentation
The Stata Journal 2015; 15(3):712–736
- Alessio Crippa, Andrea Discacciati, Nicola Orsini, and Viktor Oskarsson
Letter: coffee consumption and gallstone disease—a cautionary note on the assignment of exposure values in dose–response meta-analyses
Alimentary Pharmacology & Therapeutics 2015; in press

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List of abbreviations

AIC	Akaike Information Criterion
AL	Asymmetric Laplace
BMI	Body Mass Index
CDR	Cause of Death Register
COSM	Cohort of Swedish Men
CI	Confidence Interval
df	Degrees of Freedom
GLS	Generalized Least Squares
GRSS	Generalized Residual Sum of Squares
GTSS	Generalized Total Sum of Squares
FP2	Second-degree Fractional Polynomials
HRR	Hazard Rate Ratio
IGF-1	Insulin-like Growth Factor 1
IR	Incidence Rate
IRR	Incidence Rate Ratio
logRR	log-Relative Risk
MR	Mortality Rate
MRR	Mortality Rate Ratio
NPCR	National Prostate Cancer Register
PD	Percentile Difference
PH	Proportional-Hazards
PSA	Prostate-Specific Antigen
RAP	Risk and Rate Advancement Periods
RCS	Restricted Cubic Splines
R^2	Coefficient of Determination
RR	Relative Risk
SCB	Statistiska Centralbyrån (Statistics Sweden)
SCR	Swedish Cancer Register
SIR	Standardized Incidence Ratio
SMR	Standardized Mortality Ratio
TNM	Tumor Node Metastasis
WLS	Weighted Least Squares

Chapter 1

Introduction

“Epidemiological studies provide the only definitive information on the degree of cancer risk to man. Since malignant diseases are clearly of multifactorial origin, their investigation in man has become increasingly complex, and epidemiological and statistical studies on cancer require a correspondingly complex and rigorous methodology.”

—Lorenzo Tomatis¹

Prostate cancer was the second most common cancer in men worldwide and the most common one in developed countries in 2012 (Ferlay et al., 2015), yet its etiology remains poorly understood. To date, the only established risk factors are those that are non-modifiable: age, family history of the disease, and race/ethnicity (Grönberg, 2003).

The identification of potential modifiable risk factors is complicated by the considerable biologic heterogeneity of the disease — ranging from indolent to potentially lethal tumors — suggesting different etiologies and distinct entities (Discacciati and Wolk, 2014; Jahn et al., 2015).

Obesity is a major global public health concern, with 205 million men worldwide estimated to be obese. This obesity epidemic is particularly severe in developed countries, where, for example, as much as 20% of men living in Western Europe and 30% in the U.S. were estimated to be obese (Finucane et al., 2011).

Since body fatness is related to hormonal and metabolic changes and given that prostate cancer is a hormone-related cancer, the hypothesis of an association between obesity and prostate cancer risk — possibly depending on the aggressiveness of the disease — has been repeatedly formulated (Hsing et al., 2007).

Elucidating the possible association between obesity and prostate cancer is not only important to unravel the etiology of the disease, but it is also of public health significance, as these two medical conditions affect large proportions of the male population. In addition, the fact

¹Lorenzo Tomatis (*1929–†2007) was the Director from 1982 until 1993 of the International Agency for Research on Cancer in Lyon, France. This quotation is taken from the foreword he wrote for the book “Statistical methods in cancer research. Volume 2 — The analysis of cohort studies” (Breslow and Day, 1987).

that obesity is a largely preventable condition might provide strategies for reducing prostate cancer incidence and mortality.

As the words by Lorenzo Tomatis remind us, epidemiologic investigation cannot be separated from epidemiologic methods. Likewise, the two aims of this thesis are intertwined.

First, this thesis focuses on elucidating the association of body fatness measured during early and middle-late adulthood with localized and advanced prostate cancer incidence and mortality. This is done by analyzing primary data from a large population-based cohort study (Paper I) and by summarizing the existing epidemiologic evidence in form of aggregated data (Paper IV).

Second, this thesis deals with some methodological aspects related to the analysis of primary and aggregated data. In particular, Paper II extends the use of quantile regression for censored data to those situations where attained age is the time scale of interest, Paper III clarifies the appropriate use and interpretation of risk and rate advancement periods, while Paper V presents relevant methods for assessing the goodness of fit of dose–response meta-analysis models for binary outcomes.

Chapter 2

Background

2.1 Prostate cancer

Prostate cancer is the development of cancer in the prostate, a gland in the male reproductive system that is located just below the bladder, surrounding the urethra. More than 90% of all prostate cancers develop from the gland cells and are referred to as adenocarcinomas.

Early prostate cancer is generally asymptomatic. However, symptoms include increased frequency of urination, painful urination (dysuria), blood in the urine (hematuria), and erection dysfunction. This group of symptoms is known as lower urinary tract symptoms. If the cancer has metastasized to the bones, it can also cause bone pain, especially in the vertebrae, ribs, or pelvis.

Prostate cancer is a very heterogeneous disease, ranging from indolent and slow-growing tumors to aggressive and fast-developing tumors (figure 2.1). The majority of prostatic carcinomas are, however, slow-growing and the time period between onset and clinical presentation of the disease can span several years. Men with this subtype of disease are likely to die from unrelated causes, such as cardiovascular diseases. On the other extreme there are aggressive cancers, which grow fast and may metastasize to the bone or lymph nodes, eventually causing premature death. Figure 2.2 schematically exhibits the natural course of prostate cancer.

2.1.1 Descriptive epidemiology

Incidence

Prostate cancer was the second most common cancer in men worldwide and the most common one in more developed regions in 2012 (Ferlay et al., 2015). The age-standardized Incidence Rates (IRs) showed large geographic variation, with the highest rates observed in Australia/New Zealand (111.6 cases per 100,000 men), Northern America (97.2 cases per 100,000), and Western Europe (94.9 cases per 100,000 men). In contrast, the lowest IRs were observed in Asia (9.4 cases per 100,000 men) (figure 2.3). Geographical differences were present also within Europe, where, for example, the age-standardized IR in Sweden was estimated to be around 1.7-times times of that in Italy (Ferlay et al., 2015).

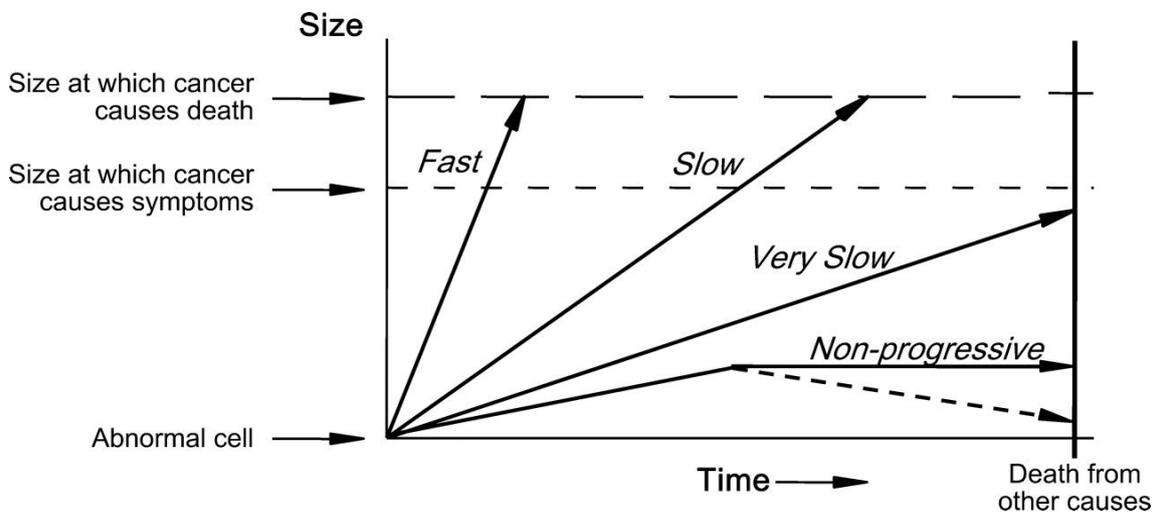


Figure 2.1: Heterogeneity of prostate cancer progression. The arrow labeled “fast” represents a fast-growing cancer, one that quickly leads to symptoms and to death. The arrow labeled “slow” represents a slow-growing cancer, one that leads to symptoms and death but only after many years. The arrow labeled “very slow” represents a cancer that never causes problems because the patient will die of some other cause before the cancer is large enough to produce symptoms. The arrow labeled “non-progressive” represents cellular abnormalities that meet the pathological definition of cancer but never grow to cause symptoms. Reproduced with permission from Welch and Black (2010).

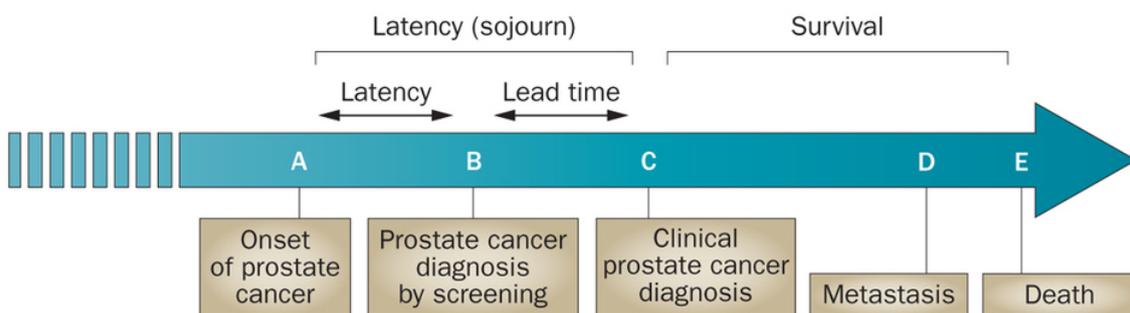


Figure 2.2: Natural history of prostate cancer. This figure illustrates the course of prostate cancer from initiation (A), to diagnosis by screening (B), to diagnosis by clinical symptoms (C), to clinically detectable metastatic disease (D), and finally to death from prostate cancer (E). Reproduced with permission from Salinas et al. (2014).

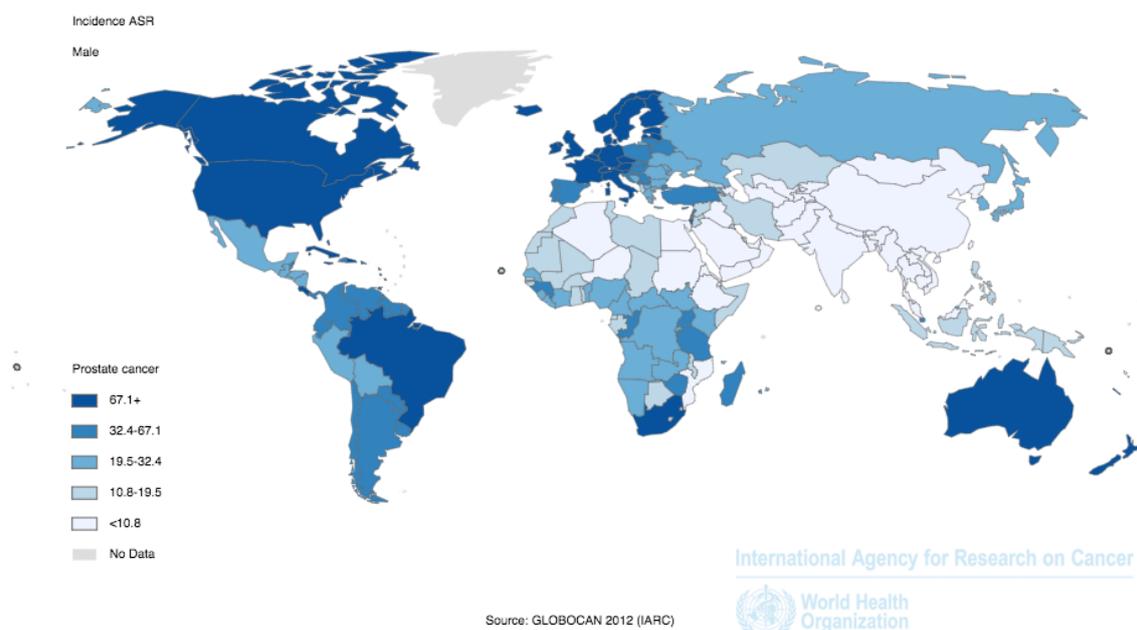


Figure 2.3: Age-standardized prostate cancer incidence rates per 100,000 men, worldwide, 2012. Rates are age-standardized to the World population. Source: GLOBOCAN 2012 (IARC).

In Sweden, the incidence of prostate cancer increased constantly during the period 1960–2004, with a steeper increase starting from the mid-1990’s, and has been stable or even slightly decreasing since then (1.5% average yearly decrease during 2004–2013) (figure 2.4). On average, around 10,000 cases were diagnosed every year during the period 2009–2013 and they amounted to 34% of the total cancer diagnoses (Engholm et al., 2015). Geographic variation is present also within Sweden, where an almost 2-fold difference in prostate cancer incidence was observed between counties according to NPCR data from 2000–2001 (Stattin et al., 2005).

Mortality

Prostate cancer was the fifth leading cause of cancer death in men worldwide in 2012, with an estimated total of 307,000 deaths (7% of the overall male cancer mortality) (Ferlay et al., 2015). Geographical variation was less pronounced for mortality than for incidence (figure 2.5). Unlike incidence, the highest age-standardized Mortality Rates (MRs) were observed in populations of African descent. However, the lowest MRs were, similarly to incidence, observed in Asia (3.8 deaths per 100,000 men). Northern America showed slightly lower age-standardized MRs as compared with Europe (9.8 versus 11.3 deaths per 100,000 men) (Ferlay et al., 2015).

In Sweden, MRs have been relatively stable over time (figure 2.4), with a 2.7% average yearly decrease during the period 2004–2013. Still, around 2,400 men died on average every year and accounted for 21% of all cancer deaths (2009–2013) (Engholm et al., 2015). The 5-year relative survival among men diagnosed with prostate cancer was around 90%, while the 10-year survival was around 80% (as of 2012), showing a steady increase over time

(Socialstyrelsen and Cancerfonden, 2013).

2.1.2 Classification

As a consequence of prostate cancer heterogeneity, its classification in risk categories at the time of diagnosis has the important objective of grouping patients with a similar prognosis. This allows primarily to make recommendations regarding their treatment, but also to compare clinical, pathological, and epidemiologic data coming from different sources.

Different classification criteria have been developed with the aim of improving risk stratification (Cooperberg et al., 2005; Boorjian et al., 2008; Heidenreich et al., 2014; Mohler et al., 2014). These criteria are generally based on a combination of Tumor Node Metastasis (TNM) staging system, Gleason grading system, and PSA serum level at diagnosis. In Sweden, the criterion used by the NPCR is based on an adapted version of the National Comprehensive Cancer Network classification scheme and has been slightly modified during the last years (NPCR, 2013) (table 2.1).

In practice, epidemiologic studies employ different and sometimes inconsistent criteria to classify prostate cancer. Moreover, the same terms are often used to refer to subtypes of cancer defined in different ways, thus complicating the interpretation and comparison of the results. For example, the term ‘advanced’ prostate cancer is variably defined as higher grade, later stage, presence of metastatic disease or death, stage C or D on the Whitmore/Jewett scale, or different combinations of these.

2.1.3 Prostate-specific antigen testing

PSA is an enzyme produced by the prostate’s epithelial cells and its primary function is to liquefy the semen in the seminal coagulum. Low PSA levels are present in the blood of healthy men and tend to increase naturally with age (Lilja et al., 2008). However, abnormally high PSA levels may be a sign of prostate cancer or other prostatic diseases, such as benign prostatic

Table 2.1: Risk categories according to the NPCR classification criteria (NPCR, 2013).

Risk category	Criterion
1. Low-risk	T1–2, Gleason Score 2–6, PSA <10 ng×ml ⁻¹
1a. Very low-risk	T1c, PSA <10 ng×ml ⁻¹ , Gleason Score 2–6, no more than 2 biopsy cores with cancer, total length of biopsies <4mm
1b. Low-risk (other)	Low-risk not categorized as 1a
1c. Low-risk (missing)	Missing information for low-risk categorization according to 1a and 1b
2. Intermediate-risk	T1–2, Gleason Score 7, <i>and/or</i> 10 ≤ PSA <20 ng×ml ⁻¹
3a. Localized high-risk	T1–2, Gleason Score 8–10, <i>and/or</i> 20 ≤ PSA <50 ng×ml ⁻¹
3b. Locally advanced	T3, PSA <50 ng×ml ⁻¹
4. Regionally metastatic	T4 <i>and/or</i> N1 <i>and/or</i> 50 ≤ PSA <100 ng×ml ⁻¹ , <i>and</i> Mx–0
5. Distant metastases	M1 <i>and/or</i> PSA ≥ 100 ng×ml ⁻¹
6. Missing	Missing information for categorization

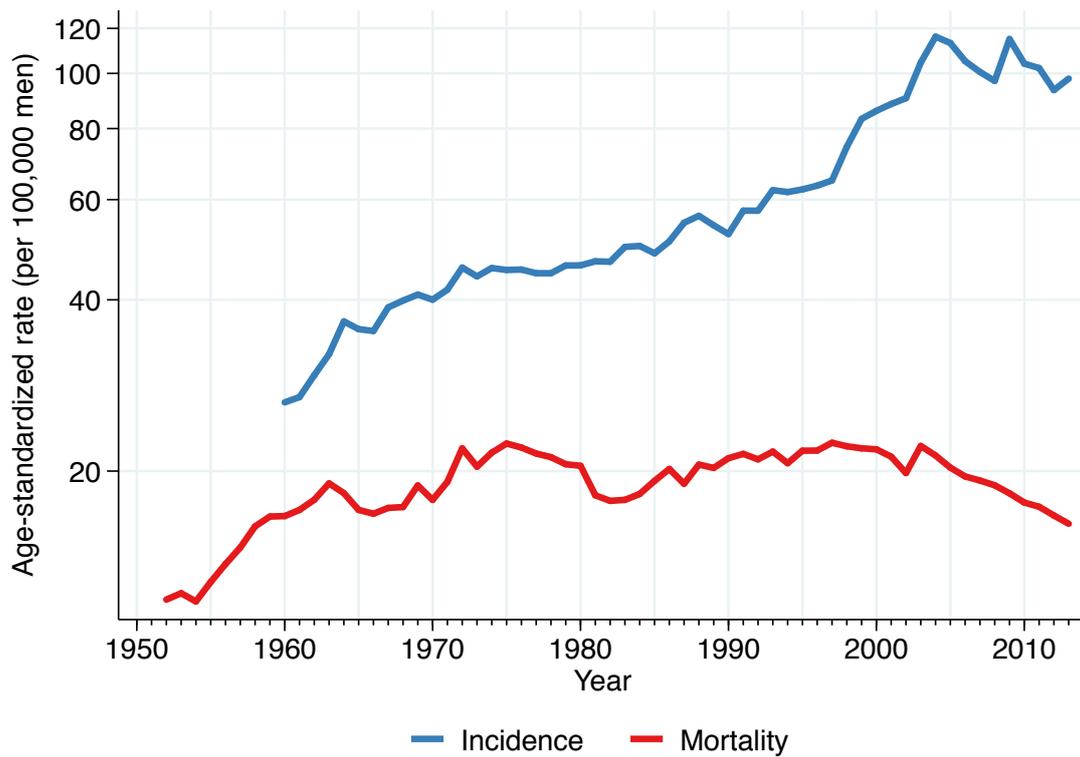


Figure 2.4: Age-standardized prostate cancer incidence and mortality rates per 100,000 men, Sweden, 1952–2013. Rates are age-standardized to the World population. The vertical axis is on the natural log scale. Data source: NORDCAN.

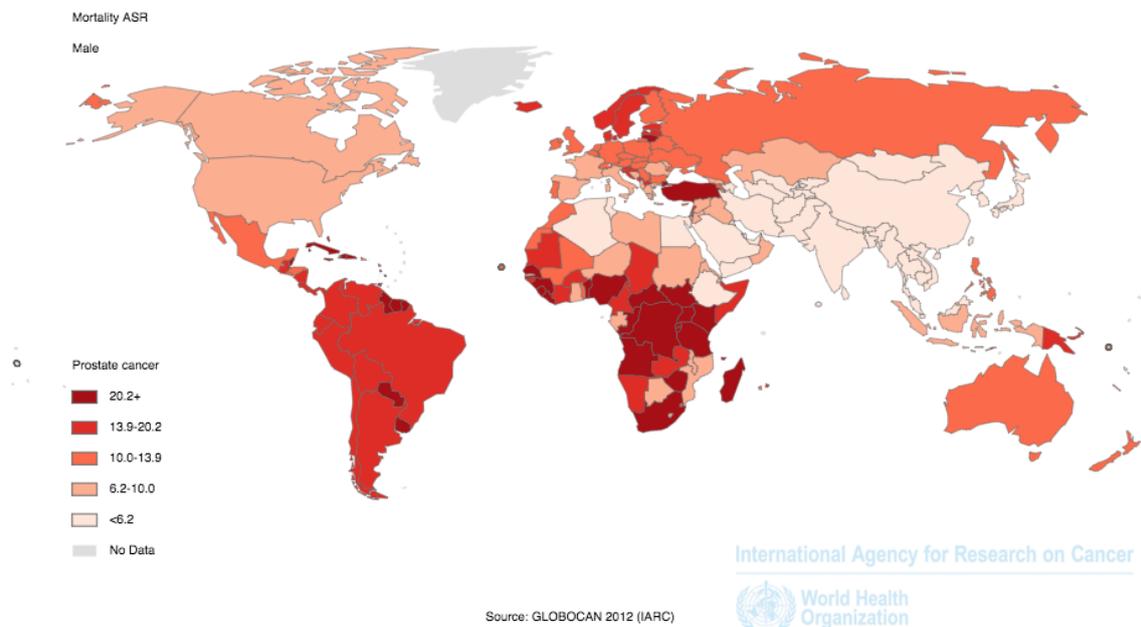


Figure 2.5: Age-standardized prostate cancer mortality rates per 100,000 men, worldwide, 2012. Rates are age-standardized to the World population. Source: GLOBOCAN 2012 (IARC).

hyperplasia or prostatitis — that is, inflammation of the prostate. This reflects the fact that this enzyme is organ-specific but not prostate cancer-specific.

In the U.S., PSA testing was introduced in the late 1980s and approved by the Food and Drug Administration as a prostate cancer diagnostic marker in 1994 (Lilja et al., 2008). The rationale behind this test is to detect prostate cancer early on, giving the possibility of intervening with curative treatments and, as a result, reduce the mortality from the disease. However, two problems related to the PSA test are its low sensitivity and the risk of overdiagnosis — that is, the diagnosis of a cancer “that would otherwise not go on to cause symptoms or death” (Welch and Black, 2010). Using data from the placebo arm of the Prostate Cancer Prevention Trial (PCPT), it was estimated that the test sensitivity is 24 and 35% for cut-offs of 3 and 4 $\text{ng}\times\text{ml}^{-1}$, respectively (Thompson et al., 2006). More in general, PSA had a discrimination ability of 0.68, as measured by the area under the ROC curve (Thompson et al., 2006). Overdiagnosis, which has been estimated to be in the range of 23–67% for prostate cancer (Draisma et al., 2009; Welch and Black, 2010), can have a major impact on a man’s life both in terms of psychological burden due to the cancer diagnosis and in terms of side effects following unnecessary treatment. Lastly, there is no conclusive evidence that PSA screening can in fact be useful to reduce prostate cancer mortality (Cuzick et al., 2014), and the two largest randomized trials on this matter — the Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) screening trial, and the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial — showed conflicting results. Namely, the PLCO trial observed no evidence of a decrease in prostate cancer mortality comparing systematic screening versus opportunistic screening, whereas the ERSPC trial observed a 21% reduction in screened versus unscreened men. A recent study using data from Swedish registers showed that more-intense PSA screening decreased prostate cancer-specific mortality as compared with opportunistic screening, which might reconcile the findings from the PLCO and ERSPC trials (Stattin et al., 2014). The value of using PSA as a screening tool in the general population remains however controversial (Cuzick et al., 2014).

Sweden does not have, to date, a national screening program for prostate cancer. Socialstyrelsen [the National Board for Health and Welfare (NBHW)] carried out an extensive literature review in 2013 and recommended against the introduction of a screening program (Socialstyrelsen, 2013).² Nevertheless, non-systematic, opportunistic PSA testing has increased over time since its introduction in the 1990s, which can explain the increase in prostate cancer incidence shown in figure 2.4 (Jonsson et al., 2011; Nordström et al., 2013; Socialstyrelsen, 2013). It has been estimated that around half of the Swedish men aged 55–69 years old are PSA-tested, with large regional differences (Jonsson et al., 2011). In the Stockholm County, the proportion of the 2011 male population that had been tested during the previous 9 years was estimated to be between 46 and 77%, depending on the age group considered (Nordström et al., 2013).

²“Hälso- och sjukvården bör inte erbjuda screening för prostatacancer med test av prostataspecifikt antigen (PSA).”

2.1.4 Risk factors

The etiology of prostate cancer is poorly understood, with the only established risk factors being age, family history of the disease, and race/ethnicity. To date, prostate cancer is not clearly linked to any preventable risk factors (Cogliano et al., 2011; Discacciati and Wolk, 2014; WCRF and AICR, 2014).

At the same time, WCRF and AICR recently updated the findings from the 2007 Second Expert Report in their 2014 Continuous Update Project. The conclusions from the 2014 report read “there is strong evidence that being overweight or obese increases the risk of advanced prostate cancer (being overweight or obese is assessed by body mass index (BMI), waist circumference and waist-hip ratio)” (WCRF and AICR, 2014). The degree of evidence for body fatness being associated with advanced prostate cancer, however, still does not reach the highest possible level of ‘strong evidence — convincing’.

Non-modifiable risk factors

Age is the strongest risk factor for prostate cancer. Diagnosis is very uncommon in men younger than 40 years old and mortality is rare before the age of 50 years. It has been estimated that only 25% of the incident cases in Europe in 2012 were diagnosed before the age of 65 years (Ferlay et al., 2015). Similarly, in Sweden, only 30% of those men who received a prostate cancer diagnosis in 2013 were younger than 65 years of age (Socialstyrelsen, 2014). Incidence of prostate cancer increases sharply after the age of 55 years, peaks around 70–74 years of age, and declines slightly thereafter (Ferlay et al., 2015). This steep trend in the age-incidence curve has been observed in multiple populations, including populations where PSA screening was completely absent (Armitage and Doll, 1954). Early-onset prostate cancer — that is, prostate cancer diagnosed in men aged less than 55 years of age — has been suggested to be a distinct phenotype, both from an etiological and clinical point of view (Salinas et al., 2014).

The risk of developing prostate cancer among men who have a first-degree relative with prostate cancer is around 2.5 times the risk among men without a diagnosed first-degree relative (Zeegers et al., 2003; Kiciński et al., 2011). This risk increases with decreasing age of the proband, with increasing number of affected relatives, and if the affected relative is a brother rather than the father. Family history is also associated to prostate cancer mortality (Brandt et al., 2010). Familial aggregation of prostate cancer is largely due to genetic factors, as suggested by twin studies, where heritability was estimated to be around 30–40% (Ahlbom et al., 1997; Lichtenstein et al., 2000; Eeles et al., 2013). In the last 10 years, more than 70 low-penetrance susceptibility loci have been identified through genome-wide association studies (Goh and Eeles, 2014). Familial aggregation can, however, be partly explained also by increased screening propensity among men with family history of prostate cancer (Bratt et al., 2010).

Racial/ethnic variation in prostate cancer risk is very pronounced, too. In the U.S., during the period 2007–2011 (most recent available data), African-American men were observed to have around 60% higher incidence and 140% higher mortality as compared with Caucasian

men. Conversely, Hispanic men had approximately 10% lower incidence and mortality (ACS, 2015). These differences are partially due to a combination of genetic and lifestyle factors, but disparities in socioeconomic status, as well as access to health care and prostate cancer screening may also contribute to explain the observed variation (Jones et al., 2008). Geographical variation is also substantial (figure 2.3). Although this geographic variability can be explained by differences in screening programs and in genetic factors, results from migrant studies support the hypothesis that lifestyle factors might play a role in prostate cancer etiology (Wilson et al., 2012).

Body mass index

Since body adiposity is related to both hormonal and metabolic pathways and since prostate cancer is a hormone-related cancer (Hsing et al., 2007), the investigation of a possible association between body fatness and prostate cancer risk has received considerable attention in epidemiologic research. The picture regarding this potential association has become clearer and more nuanced during the last 10 years or so.

BMI is probably the most common proxy for body adiposity in epidemiologic studies.³ In fact, weight and height can be measured relatively simply and accurately even in large populations unlike waist circumference or waist-to-hip ratio. BMI may be inadequate to measure body adiposity for a single individual, but it has been observed to correspond reasonably well with percentage body fat within sex and age groups (Flegal et al., 2009).

By the late 2011,⁴ the existing body of literature on BMI and total prostate cancer was quite extensive, but at the same time results were inconsistent. In particular, the largest meta-analysis available to that date, which included 27 prospective studies for a total of more than 70 thousand prostate cancer cases, observed no evidence of an association between BMI and total prostate cancer [Relative Risk (RR) for every 5-unit increment: 1.03 (95% Confidence Interval (CI): 0.99–1.06)]⁵ and a high between-study heterogeneity (Renehan et al., 2008). Similarly, the 2007 Second Expert Report published by WCRF and AICR observed no evidence of an association, based on 24 prospective studies [RR for every 5-unit increment: 1.00 (95% CI: 0.99–1.01)]. As a consequence, body fatness was listed among those factors for which no conclusions could be reached (strength of the evidence: ‘limited — no conclusion’) (WCRF and AICR, 2007, section 7.14).

The hypothesis that the association between body adiposity and prostate cancer risk could differ according to the aggressiveness of the disease — therefore suggesting etiological heterogeneity of prostate cancer related to obesity — repeatedly appeared in the literature during those years (Freedland et al., 2006a; Freedland and Platz, 2007; Hsing et al., 2007, 2008). The available epidemiologic evidence supported this intriguing hypothesis, but at the same time it

³BMI is calculated as $\text{kg} \times \text{m}^{-2}$ — that is, weight in kilograms multiplied by height in meters to the power of minus 2.

⁴The beginning of my graduate studies.

⁵The term ‘relative risk’ will be used in this thesis as a generic term for the risk ratio, hazard rate ratio, incidence rate ratio, or odds ratio.

was still limited. In fact, just a few studies had looked into the association between body adiposity and prostate cancer by subtype of the disease. As a result, the only available meta-analysis that carried out separate analyses by subtype of prostate cancer included 4 case-control and 6 prospective studies (two of which were very small), for a total of less than 2 thousand cases. Despite this, a positive association between BMI and the risk of advanced prostate cancer was observed [RR for every 5-unit increment: 1.12 (95% CI: 1.01–1.23)] (MacInnis and English, 2006).

During the years following the meta-analysis by MacInnis and English (2006) and the Second Expert Report (WCRF and AICR, 2007), a considerable amount of epidemiologic research on body adiposity and prostate cancer has been carried out, including Paper I of this thesis. Furthermore, epidemiologic studies started to systematically report results separately by specific subtypes of prostate cancer, although with the limitations described in section 2.1.2, allowing a clearer picture to emerge. Paper IV was the first meta-analysis after the one published by MacInnis and English (2006) to summarize the available evidence on BMI and prostate cancer risk by subtype of the disease. In particular, Paper IV was considerably larger, including 13 prospective studies and about 6 times the number of prostate cancer cases. Results showed an increased risk of advanced prostate cancer [RR for every 5-unit increment: 1.09 (95% CI: 1.02–1.16)] and a decreased risk of localized prostate cancer [RR for every 5-unit increment: 0.94 (95% CI: 0.91–0.97)]. Lastly, the 2014 Continuous Update Project report showed very similar results to those of Paper IV for advanced prostate cancer [RR for every 5-unit increment: 1.08 (95% CI: 1.04–1.12)], while a non-linear association was observed for localized prostate cancer (WCRF and AICR, 2014). An overview of the results from meta-analyses on BMI and prostate cancer incidence — including the updated dose–response meta-analysis based on Paper IV and described in section 5.4.2 — is reported in table 2.2.

In conclusion, the official recommendations issued in 2014 by the WCRF and ARIC read “to reduce the risk of developing advanced prostate cancer, we recommend maintaining a healthy weight” (WCRF and AICR, 2014).

Given that prostate cancer has usually a long latency period, spanning even decades between tumor initiation and diagnosis, body adiposity earlier in life could in theory play an important role in tumor initiation and development. Moreover, the prostate may be more susceptible to carcinogenic exposures during the developmental stages and immediately thereafter (Sutcliffe and Colditz, 2013). For these reasons, BMI during childhood, puberty, and early adulthood — defined as ages between 18 and 30 years — has been investigated by epidemiologic studies, including Paper I of this thesis. The results, however, are inconsistent (Sutcliffe and Colditz, 2013).

Table 2.2: Results from dose-response meta-analyses on BMI and incidence of prostate cancer.

Outcome	Year	Authors	Number of studies	RR ^{a,b}	95% CI
Total prostate cancer	2007	WCRF and AICR	24 cohort	1.00	0.99-1.01
	2008	Renehan et al.	27 cohort	1.03	0.99-1.06
	2014	WCRF and AICR	39 cohort	1.00	0.97-1.03
Localized prostate cancer	2006	Maclinnis and English	6 cohort and 4 case-control	0.96	0.89-1.03
	2012	Discacciati et al. (Paper IV)	12 cohort	0.94	0.91-0.97
	2014	WCRF and AICR	14 cohort	— ^{c,d}	—
	2015	Discacciati (Paper IV, updated)	14 cohort	— ^{c,e}	—
	2006	Maclinnis and English	6 cohort and 4 case-control	1.12	1.01-1.23
Advanced prostate cancer	2012	Discacciati et al. (Paper IV)	13 cohort	1.09	1.02-1.16
	2014	WCRF and AICR	23 cohort	1.08	1.04-1.12
	2015	Discacciati (Paper IV, updated)	18 cohort	1.07	1.03-1.12
	2006	Maclinnis and English	6 cohort and 4 case-control	1.12	1.01-1.23

^a For every 5-unit increment in BMI.

^b Results are from random-effect meta-analyses.

^c No RR for every 5-unit increment in BMI was calculated, as there was evidence of a non-linear relationship.

^d The RRs for 25, 31, and 37 kg×m⁻² versus 21 kg×m⁻² were 1.04 (95% CI: 1.02-1.05), 0.94 (95% CI: 0.92-0.96), and 0.79 (95% CI: 0.75-0.83), respectively ($P_{\text{non-linearity}} < 0.01$).

^e The RRs for 25, 30, and 35 kg×m⁻² versus 22 kg×m⁻² were 1.01 (95% CI: 0.99-1.04), 0.93 (95% CI: 0.90-0.98), and 0.81 (95% CI: 0.74-0.88), respectively ($P_{\text{non-linearity}} < 0.001$).

2.2 Survival analysis of primary data

Survival analysis refers to the analysis of time from a specific time point until the occurrence of a well-defined event (survival time).⁶ A unique characteristic of survival data is that observations may be censored — that is, for some study individuals the event time is unknown. There are different censoring mechanisms, but right-censoring — arguably the most common in epidemiologic studies — is the only type of censoring considered in this thesis. Furthermore, we will make the assumption that survival time and censoring time are independent, possibly conditional on a vector of known, fixed covariates.

With no censoring, survival time can be analyzed as any other numeric variable, for example using Wilcoxon’s rank-sum test or standard quantile regression. When censoring is present, a number of statistical tools is available to deal with this mechanism. However, one should always remember that the ultimate goal is to describe the distribution of survival time, and how this is affected by a vector of covariates.

Lastly, the term ‘primary data’ (or ‘individual patient data’) refers to the availability of raw data for each participant in an epidemiologic study or clinical trial, as opposed to aggregated data.

2.2.1 Basic statistical concepts

The statistical concepts introduced in this section are standard and therefore only a brief overview will be given. See for example Kleinbaum and Klein (2012) for a more rigorous and detailed exposition.

Let T be a continuous, non-negative random variable with probability density function (p.d.f.) $f(t)$, and cumulative density function (c.d.f.) $F(t) = \Pr(T \leq t)$, which gives the probability that the event has occurred by time t . Usually, one observes the possibly right-censored random variable $Y = \min(T, C)$, where C is the censoring random variable. In addition to the p.d.f. and the c.d.f., there are three alternative but equivalent functions to describe the distribution of T . These are the survival function, the hazard function, and the cumulative hazard function.

The survival function $S(t)$ gives the probability that the survival time is larger than t — that is, the probability of being event-free at time t . It is a non-decreasing function of t and can take values between 0 and 1. $S(t)$ is equal to 1 minus the c.d.f.:

$$S(t) = \Pr(T > t) = 1 - F(t) = \int_t^{+\infty} f(s)ds. \quad (2.1)$$

A common non-parametric estimator for the survival function is the Kaplan-Meier product-limit estimator (Kaplan and Meier, 1958).

A different characterization of the distribution of T is given by the hazard function $h(t)$,

⁶The terms ‘event’, ‘outcome’, and ‘disease’ are equivalent and therefore they are used interchangeably in this thesis.

which is defined as:

$$h(t) = \lim_{dt \rightarrow 0} \frac{\Pr(t < T \leq t + dt | T > t)}{dt}. \quad (2.2)$$

The numerator of the hazard function is the conditional probability that the event of interest will happen in the time interval $(t, t + dt)$, given that it has not occurred before. The denominator is the width dt of such a time interval. By dividing the first by the second, one obtains the event rate per unit of time, and taking the limit as dt goes to 0, the instantaneous event rate. Therefore, $h(t)dt$, for an infinitesimal dt , is akin to the conditional probability that the event will occur in the time interval $(t, t + dt)$ given $S(t)$. However, the hazard itself is not a probability (and in fact it is not bounded between 0 and 1). The key feature of the hazard function is its conditional nature. Contrast, for example, the unconditional probability, for all the men born on a given year, of dying after 40 years of age [$S(40)$], with the probability of dying in the time interval $(39 < T \leq 40 \text{ years} | \text{alive at 39 years})$. For example, $S(40)$ was estimated to be around 60% for men born in 1861 in Sweden. However, given survival up to 39 years of age, the probability of being alive at age 40 years was much higher, roughly 98% (SCB, 2010).

Lastly, the cumulative hazard function is the integrated hazard function:

$$H(t) = \int_0^t h(s)ds.$$

All the functions described above are mathematically related and in particular,

$$S(t) = \exp(-H(t)) = \exp\left(-\int_0^t h(s)ds\right). \quad (2.3)$$

2.2.2 The proportional-hazards approach to survival modeling

In the previous section we focused on how to characterize the distribution of T . However, a major objective in epidemiologic research is to describe the variation in the distribution of T — and therefore in survival — among individuals, given a vector of covariates. Different “classical” approaches to survival modeling are available, the most common probably being Accelerated Failure Time models and proportional-hazards (PH) models. An additional approach was recently introduced by Royston and Parmar (2002).⁷ In this section we will give a brief overview of the PH model. The literature on this topic is enormous and the reader can refer for example to Therneau and Grambsch (2000), Kalbfleisch and Prentice (2002), and van Houwelingen and Stijnen (2013) for a more complete discussion.

The proportional-hazards model

The PH model focuses directly on the hazard function. In particular, the hazard at time t , for a given individual i with covariate vector $\mathbf{x}_i = (x_{i1}, \dots, x_{ik})$ (not including a constant), is

⁷Royston-Parmar models include, but are not limited to, PH models.

assumed to be:

$$h_i(t|\mathbf{x}_i) = h_0(t) \exp(\mathbf{x}_i^\top \boldsymbol{\beta}), \quad (2.4)$$

where $h_0(t)$ is the baseline hazard for all individuals with $\mathbf{x}_i = (0, \dots, 0)$, $\boldsymbol{\beta} = (\beta_1, \dots, \beta_k)$ is the vector of unknown model coefficients, and $\exp(\mathbf{x}_i^\top \boldsymbol{\beta})$ is a proportional (multiplicative) increase or reduction of the baseline hazard associated with the covariates \mathbf{x}_i — that is, the Hazard Rate Ratio (HRR). Of note, this proportional increase or reduction in baseline hazard is constant over t . In other words, PH models assume that the relative effect of a covariate is the same at all time points.

An immediate consequence of models written in the form of equation (2.4), is that the cumulative hazards are proportional too. In fact, integrating both sides of the equation from 0 to t gives the following result:

$$H_i(t|\mathbf{x}_i) = \int_0^t h_0(s) \exp(\mathbf{x}_i^\top \boldsymbol{\beta}) ds = H_0(t) \exp(\mathbf{x}_i^\top \boldsymbol{\beta}). \quad (2.5)$$

Moreover, given equation (2.3), the following relation for the survival function is immediately obtained:

$$S_i(t|\mathbf{x}_i) = S_0(t)^{\exp(\mathbf{x}_i^\top \boldsymbol{\beta})}. \quad (2.6)$$

This important result says that, for PH models, the effect of the covariate vector \mathbf{x}_i on the survival function is to raise $S_0(t)$ (the baseline survival function) to a power equal to the constant $\exp(\mathbf{x}_i^\top \boldsymbol{\beta})$. As Kalbfleisch and Prentice (2002, pg. 118) pointed out “note that the assumed model constraints the estimates so that one survivor function dominates the other. Such graphs can give a misleading impression that one of the treatments is consistently preferable and suggest significant differences even when they are not present.”

Time-dependent coefficients

The PH model lends itself to extensions, such as time-varying covariates and time-dependent coefficients. In particular, time-dependent coefficients are useful to relax the assumption of proportionality of the hazards over time. To accommodate time-dependent coefficients, the PH model can be rewritten as:

$$h_i(t|\mathbf{x}_i) = h_0(t) \exp(\mathbf{x}_i^\top \boldsymbol{\beta}(t)), \quad (2.7)$$

and the time-dependent coefficients are modeled using b transformations of time. For example, suppose that only one coefficient $\beta(t)$ is included in the model, then

$$\beta(t) = \sum_{j=1}^b \gamma_j g_j(t). \quad (2.8)$$

This extended model — sometimes referred to as ‘extended PH model’ or ‘general hazard rate model’ — implies that the HRR is free to vary over time (time-dependent HRR). Another

consequence is that the simple equation (2.6) does not longer apply, as the coefficients are now a function of time and therefore they cannot be taken out of the integral in equation (2.5). The survival curve for the i -th individual is now given by:

$$S_i(t|\mathbf{x}_i) = \exp\left(-\int_0^t h_0(s) \exp(\mathbf{x}_i^\top \boldsymbol{\beta}(s)) ds\right). \quad (2.9)$$

Calculation of the survival curve is still possible, but is now more complicated. The integral in equation (2.9) can be derived analytically (in simple parametric situations) or numerically, as a cumulative sum of predictions. The latter approach is described in detail by Carstensen (2005, section 4). The complexity in the calculation of model-based survival curves is certainly a drawback of PH models with time-dependent coefficients. At the same time, one should keep in mind that these models put the focus on the HRR, which on the other hand is quite simple to calculate even in the presence of time-dependent coefficients (Heinzl and Kaider, 1997).

The consequences on the HRR of the omission of time-dependent coefficients when actually needed are numerous in the literature (see, for example, Royston and Parmar, 2011; Uno et al., 2014). Figure 2.6, on the other hand, shows an example of such consequences on model-based predicted survival curves. In particular, in panel A the hazards were forced to be proportional [equation (2.6) for the survival curves applies], whereas in panel B this assumption was relaxed by including a time-dependent coefficient [equation (2.9) for the survival curves applies].

Model fitting

There are different possible approaches to fitting hazard rate models.

The first is the ‘pure’ parametric approach, where the time variable T is assumed to follow a specific distribution. Consequently, a specific functional form is assumed for the baseline hazard $h_0(t)$. Examples of distributions used to characterize T are the exponential, Weibull, and Gompertz distribution.

The second approach might be referred to as the ‘flexible’ parametric approach.⁸ With this approach, time is split into non-overlapping intervals and the assumption that the baseline hazard $h_0(t)$ is constant within each interval is made, leading to a so-called piece-wise exponential model. If time is split finely enough, one can use a smooth, flexible function of time to model $h_0(t)$. Time-dependent HRRs are easily accommodated by including interactions (product terms) between covariates and transformations of time.⁹ Since an exponential distribution for T is assumed within each time interval, these models are closely related to Poisson regression (Breslow and Day, 1987, section 4.2).

The third approach is the ‘semi-parametric’ approach, where the association between the covariates and the hazard is modeled parametrically — similarly to the other two approaches — but the baseline hazard $h_0(t)$ is left unspecified. This approach is based on a partial likelihood

⁸Not to be confused with the flexible parametric survival model by Royston and Parmar (Royston and Parmar, 2002; Royston and Lambert, 2011), which is not covered in this thesis.

⁹This shows that, practically, models with time-dependent coefficients can be handled in the same way as models with time-varying covariates (van Houwelingen and Stijnen, 2013).

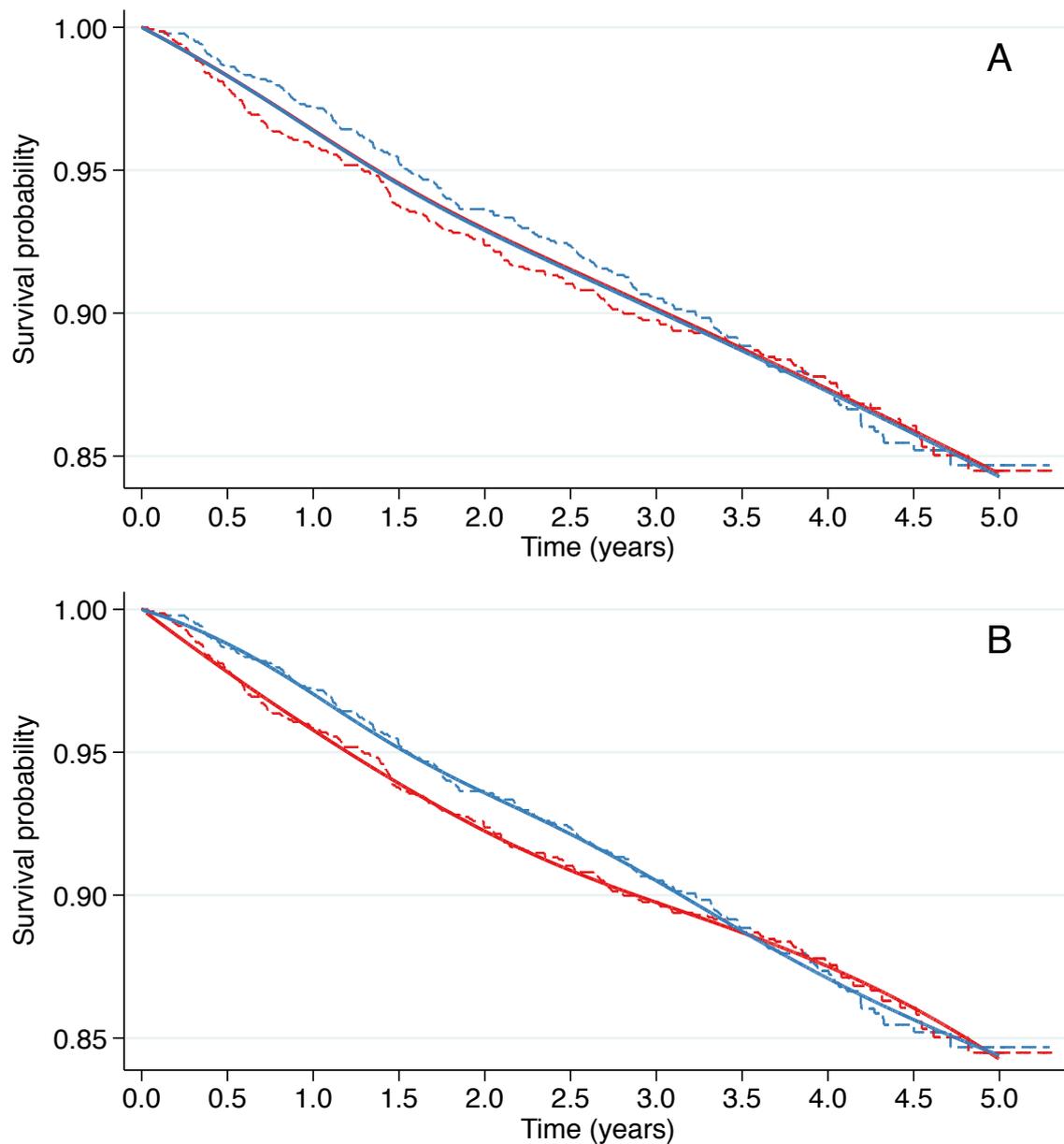


Figure 2.6: Consequences of the violation of the PH assumption on the predicted survival curves. In panel A, a PH model without time-dependent coefficients was employed. The model-based predicted survival curves for women in the active treatment (red solid line) and in the placebo arm (blue solid line) were far off from the corresponding non-parametric Kaplan-Meier estimates (dashed lines). In panel B, the time-dependent coefficient for the binary variable indicating the treatment group was modeled using restricted cubic splines with 5 knots. As a result, the model-based predicted survival curves followed closely the corresponding non-parametric estimates. Note how in panel B the model-based survival curves cross after around 3.5 years, following the behavior of the Kaplan-Meier estimates. See Hulley et al. (1998) for more information about the data.

function introduced by Cox (1972). Non-parametric estimates, following a Cox model, of the baseline survival function and of the cumulative hazard function can be calculated as described by Kalbfleisch and Prentice (2002, section 4.3). A smooth estimate of the baseline hazard can then be obtained by smoothing the cumulative hazard function using a kernel estimator as described for example in Breslow and Day (1987, section 5.3) and Cleves et al. (2010, section 8.4), or by simple parametric modeling of the estimated cumulative hazard function (Royston, 2011).

The boundaries between the approaches described above are not clear-cut. In fact, the ‘flexible’ parametric approach is ultimately a ‘pure’ parametric approach. Likewise, conditional Poisson regression is equivalent to Cox regression — that is, the contribution of each subject to the the profile log-likelihood for β of a Poisson model, where time is split at each failure time, is the same as the contribution of the j -th event time to the partial log-likelihood of a Cox model. This extends to the more general case where tied events are present (Carstensen, 2005; Royston and Lambert, 2011).

2.2.3 The percentile approach to survival modeling

Due to the widespread use of PH models, the HRR — time-varying or otherwise — has become the standard summary for comparing the survival between different groups of individuals. An alternative, complementary approach to compare such differences is to focus on survival percentiles and, specifically, on percentile differences (PDs).

Survival percentiles

The $100p$ -th survival percentile of the previously defined random variable variable T is the time t by which $100p\%$ of the study population has experienced the event of interest (where $0 < p < 1$ is the survival quantile). For example, 25th survival percentile is the time t by which 25% of the study population has experienced the event. Likewise, one could say that a randomly selected individual from this study population has 0.25 probability of experiencing the event within time t (and consequently 0.75 probability of experiencing it after time t). Therefore, survival percentiles provide the link between a given probability of experiencing the outcome and the time by which that probability is reached.

More formally, the $100p$ -th survival percentile is defined as:

$$Q_T(p) = \inf \{ t : \Pr(T \leq t) \geq p \}.$$

The function $Q_T(\cdot)$ is the quantile function, and is defined as that function such that $1 - S(Q_T(p)) = F(Q_T(p)) = p$, where $F(\cdot)$ is the c.d.f. of T introduced at the beginning of section 2.2.1. Of note, not all the survival percentiles are always estimable. It is not possible for example to calculate the 25th survival percentile for the survival curves presented in figure 2.7. This is because at the end of the follow-up time, only around 15% of the individuals had experienced the event of interest (coronary heart disease). However, all the percentiles up to

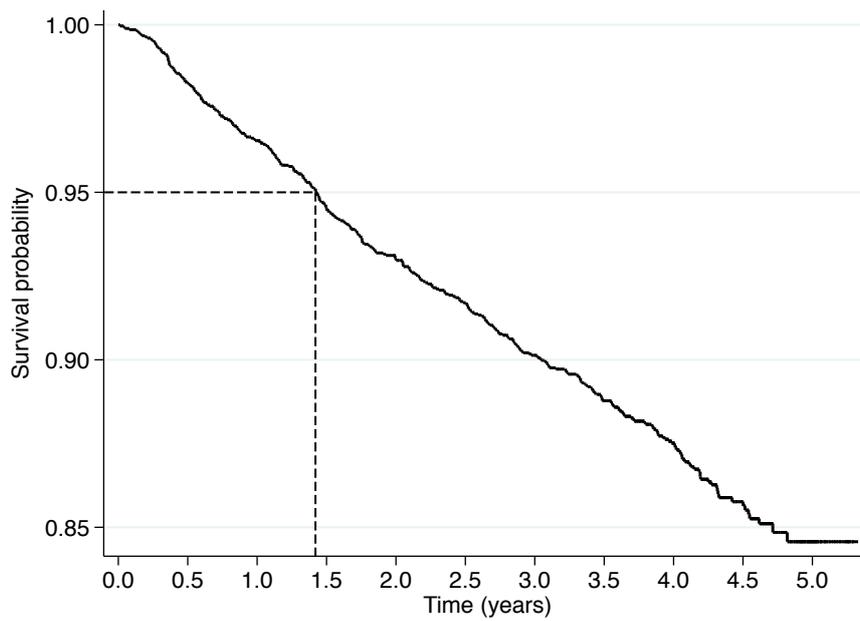


Figure 2.7: Non-parametric survival curve estimate for all the women enrolled in the HERS trial (solid line) (Hulley et al., 1998). The dashed line illustrates the 5th survival percentile (around 1.4 years).

the 15th are estimable. For example, the 5th survival percentile obtained from the Kaplan-Meier estimate of the survival curve was around 1.4 years (dashed line).

One might want to estimate the $100p$ -th survival percentile conditional on a given covariate vector \mathbf{x} . In this case, the definition of survival percentiles easily extends to:

$$Q_T(p|\mathbf{x}) = \inf \{ t : \Pr(T \leq t|\mathbf{x}) \geq p \},$$

and comparisons between groups of individuals (for example, exposed and unexposed) in terms of time elapsed before a certain proportion of individuals has experienced the event can be made. For example, in figure 2.6, the 5th survival percentile for those women in the active treatment arm (red dashed line) was around 1.3 years, whereas the same percentile was around 1.6 years for those women in the placebo arm (blue dashed line). As a result, the 5th PD between the placebo and treatment arm was 0.3 years. On the other hand, the 15th PD was practically equal to 0 years.

A statistical method that combines the flexibility of a modeling approach with the simplicity of focusing directly on survival percentiles is quantile regression for censored data.

Quantile regression for censored data

The idea behind quantile regression for censored data is to link the conditional $100p$ -th survival percentile $Q_{T_i}(p|\mathbf{x}_i)$ to the covariate vector $\mathbf{x}_i = (x_{i1}, \dots, x_{ik})$ (generally including an

intercept) though a linear, additive model. In particular:

$$Q_{T_i}(p|\mathbf{x}_i) = \mathbf{x}_i^\top \boldsymbol{\beta}(p) = \sum_{j=0}^k \beta_j(p)x_{ij}. \quad (2.10)$$

Some considerations regarding this model are necessary. First, the notation $\boldsymbol{\beta}(p)$ underlines the important characteristic that the model coefficients are not constrained to be equal for different survival percentiles. Therefore, no assumptions similar to the proportionality of the hazards are made.

Second, the linear predictor $\mathbf{x}_i^\top \boldsymbol{\beta}(p)$ can include flexible transformations of continuous covariates (such as splines of fractional polynomials), product terms, and the like. This model is perfectly suited for the analysis of epidemiologic data, where it is important to be able to model continuous covariates and adjust for confounding.

Third, by estimating multiple percentiles, one can thoroughly describe the distribution of T , conditionally on \mathbf{x} .

Fourth, the interpretation of the coefficients is particularly useful and straightforward, and it is strictly related to how one would interpret the coefficients of a classical linear regression. For example, just like in linear regression one would interpret a coefficient for a continuous variable z as “the change in the mean response variable for every 1-unit increase in z , adjusting for the other covariates in the model”, the interpretation of a similar coefficient from a quantile regression for survival data is “the change in the $100p$ -th survival percentile for every 1-unit increase in z , adjusting for the other covariates in the model”. The model coefficients are, in other words, PDs (and therefore absolute measures of association).¹⁰

Lastly, and most importantly, the model coefficients are now expressed in the metric of time, which means that they provide an intuitive measure of association between the covariates and the event of interest. This in contrast with the HRR, which is a dimensionless measure of association and possibly more difficult to interpret (Uno et al., 2014).

Different methods have been proposed to deal with the model-based estimation of conditional percentiles when data is censored (Powell, 1986; Portnoy, 2003; Peng and Huang, 2008; Wang and Wang, 2009; Bottai and Zhang, 2010). A description of the methods by Powell, Portnoy, and Peng and Huang can be found in Koenker (2008). In this thesis and in Paper II, however, we will deal with the approach developed by Bottai and Zhang (2010) and known as ‘Laplace regression’.

Laplace regression

Re-introducing the notation used before, let $Y_i = \min(T_i, C_i)$ be the observed survival time measured on the i -th out of n individuals. Moreover, let d_i be indicator variable which takes value 1 if the survival time Y_i is not censored and value 0 otherwise.

¹⁰With the usual exception regarding the coefficient for the intercept, for the product terms, and for splines or other non-linear transformations of continuous variables.

Assume that

$$T_i = \mathbf{x}_i^\top \boldsymbol{\beta}(p) + \epsilon_i, \quad (2.11)$$

where \mathbf{x}_i is the covariate vector, $\boldsymbol{\beta}(p)$ is the vector of unknown model coefficients, and ϵ_i are independently and identically distributed errors that follow a standard Laplace distribution, which is equivalent to an asymmetric Laplace (AL) distribution with location parameter 0 and scale parameter 1. For any given p , the p -th quantile of the conditional distribution of T_i given \mathbf{x}_i is $\mathbf{x}_i^\top \boldsymbol{\beta}(p)$ — that is, $Q_{T_i}(p|\mathbf{x}_i) = \Pr(T_i \leq \mathbf{x}_i^\top \boldsymbol{\beta}(p)|\mathbf{x}_i) = p$ (Bottai and Zhang, 2010).

The AL distribution has a location parameter $\mu(p)$ and a scale parameter $\sigma(p)$. This notation underlines the fact that, in the specific situation presented in this thesis, p is not a parameter to be estimated, rather it is treated as fixed. The AL distribution has the following p.d.f.:

$$f_{\text{AL}}(s) = \frac{p(1-p)}{\sigma(p)} \exp\left(-\frac{s - \mu(p)}{\sigma(p)} [p - I(s \leq \mu(p))]\right), \quad (2.12)$$

where $\sigma(p) > 0$, $-\infty < \mu(p) < +\infty$, and $I(\cdot)$ is the indicator function (Yu and Zhang, 2005).

Therefore, since the asymmetric Laplace in (2.12) is a location-scale family of densities, T_i follows an AL distribution with p.d.f conditional to \mathbf{x}_i equal to:

$$f_{\text{AL}}(t_i|\mathbf{x}_i) = \frac{p(1-p)}{\sigma(p)} \exp\left(-\frac{t_i - \mathbf{x}_i^\top \boldsymbol{\beta}(p)}{\sigma(p)} [p - I(t_i \leq \mathbf{x}_i^\top \boldsymbol{\beta}(p))]\right), \quad (2.13)$$

and c.d.f.

$$F_{\text{AL}}(t_i|\mathbf{x}_i) = \exp\left(-\frac{t_i - \mathbf{x}_i^\top \boldsymbol{\beta}(p)}{\sigma(p)} [p - I(t_i \leq \mathbf{x}_i^\top \boldsymbol{\beta}(p))]\right) [p - I(t_i > \mathbf{x}_i^\top \boldsymbol{\beta}(p))] + I(t_i > \mathbf{x}_i^\top \boldsymbol{\beta}(p)) \quad (2.14)$$

as derived by Bottai and Zhang (2010). The subscript AL in $f_{\text{AL}}(\cdot)$ and $F_{\text{AL}}(\cdot)$ is used to distinguish these functions from the p.d.f. and c.d.f. of T , respectively. Heteroskedasticity of the error term can be accommodated by allowing the scale parameter $\sigma(p)$ to depend on a vector of covariates.

The contribution to the likelihood function L of an uncensored observation ($d_i = 1$) is given by the p.d.f. in (2.13) evaluated at the observed survival time y_i — that is $L_i = f_{\text{AL}}(y_i)$. On the other hand — under the assumption of non-informative censoring conditionally on \mathbf{x}_i — a censored observation ($d_i = 0$) carries only the information that his/her event time t_i is larger than y_i . The contribution to the likelihood function is therefore $L_i = 1 - F_{\text{AL}}(y_i)$. Consequently, the likelihood function is proportional to:¹¹

$$L(\boldsymbol{\beta}(p), \sigma(p); y_i, \mathbf{x}_i, d_i) = \prod_{i=1}^n f_{\text{AL}}(y_i|\mathbf{x}_i)^{d_i} (1 - F_{\text{AL}}(y_i|\mathbf{x}_i))^{(1-d_i)}.$$

¹¹Note that this way of constructing the likelihood function also applies to parametric PH models under conditional independent right-censoring. See for example Lawless (2003, chapter 5) or Kalbfleisch and Prentice (2002, chapter 3).

The log-likelihood function is obtained as usual by taking the logarithm of the likelihood:

$$l(\boldsymbol{\beta}(p), \sigma(p); y_i, \mathbf{x}_i, d_i) = \sum_{i=1}^n [d_i \log f_{\text{AL}}(y_i | \mathbf{x}_i) + (1 - d_i) \log (1 - F_{\text{AL}}(y_i | \mathbf{x}_i))]. \quad (2.15)$$

Lastly, by substituting equations (2.13) and (2.14) in (2.15), and after some algebraic manipulations, the log-likelihood function becomes:

$$\begin{aligned} l(\boldsymbol{\beta}(p), \sigma(p); y_i, \mathbf{x}_i, d_i) = & d_i \left[-\frac{y_i - \mathbf{x}_i^\top \boldsymbol{\beta}(p)}{\sigma(p)} (p - I(y_i \leq \mathbf{x}_i^\top \boldsymbol{\beta}(p))) + \log \frac{p(1-p)}{\sigma(p)} \right] \\ & + (1 - d_i) I(y_i \leq \mathbf{x}_i^\top \boldsymbol{\beta}(p)) \log \left[1 - p \exp \left((1-p) \frac{y_i - \mathbf{x}_i^\top \boldsymbol{\beta}(p)}{\sigma(p)} \right) \right] \\ & + (1 - d_i) (1 - I(y_i \leq \mathbf{x}_i^\top \boldsymbol{\beta}(p))) \left[\log(1-p) - p \frac{y_i - \mathbf{x}_i^\top \boldsymbol{\beta}(p)}{\sigma(p)} \right]. \end{aligned} \quad (2.16)$$

The maximum likelihood (ML) estimators for the model parameters $\hat{\boldsymbol{\beta}}(p)$ and $\hat{\sigma}(p)$ are defined as the maximizers of the log-likelihood (2.16), which can be directly maximized using, for example, the gradient search algorithm recently proposed by Bottai, Orsini, and Geraci (2015). Inference on the parameters can be obtained through bootstrapping, as initially proposed in Bottai and Zhang (2010), or following standard asymptotic theory, as shown in Bottai and Orsini (2013).

Note that when censoring occurs with zero probability before the survival percentile being estimated, Laplace regression reduces to traditional quantile regression (Bottai and Zhang, 2010).

Thanks also to the development of a user-friendly command to estimate Laplace regression with Stata (Bottai and Orsini, 2013), quantile regression for censored data has been repeatedly employed in the recent years to analyze survival data in epidemiology (see, for example, Rizzuto et al., 2012; Bellavia et al., 2014; Rahman et al., 2014). Moreover, quantile regression for censored data has been proposed as a tool to evaluate additive interaction in survival analysis (Bellavia et al., 2016), and to estimate conditional and marginal survival curves (Bellavia et al., 2015a).

Lastly, we recently proposed to use quantile regression for censored data — and in particular Laplace regression — as a flexible and intuitive approach to estimate survival percentiles of age at the event (for example, age at prostate cancer death). This extends the use of this statistical tool, especially in epidemiologic research. In fact, investigators are often more interested in describing the distribution of age at the event for a group of individuals rather than the distribution of time elapsed between some arbitrary baseline event (for example, filling in a questionnaire) and the occurrence of a disease (Paper II).

2.2.4 Risk and rate advancement periods

One of the most interesting features of quantile regression is probably that the exposure-outcome association is expressed in the metric of time as PDs. Other methods have been proposed in the literature to express the impact of an exposure on the time of disease onset, such as risk and rate advancement periods (RAP) or ‘expected years of (disease-free) life lost’.

RAP, in particular, was introduced by Brenner, Gefeller, and Greenland (1993) to measure the age difference at which exposed subjects reach the same rate/risk as unexposed subjects, assuming a monotonic increase in event rate/risk over age, independence of the outcome of interest from competing risks, and conditional on disease-free survival to some baseline age. In this section we will refer to the rate advancement period only.¹² The risk advancement period is defined in a similar fashion and is presented in Paper III.

This measure has been recently given special attention by the CHANCES consortium,¹³ which is an international pooling project of primary data from cohort studies [including the Cohort of Swedish Men (COSM), see section 4.1] (Boffetta et al., 2014). The quantification of RAP to assess the impact of health-related characteristics on chronic diseases (including cancer) and overall mortality is the principal research aim of published papers (Mons et al., 2015; Müezzinger et al., 2015) and research proposals (Orsini, personal communication).

Definition

Suppose one wants to assess in a cohort study the association between an exposure e and the rate R of a binary event of interest d . Let $h(a, e, \mathbf{c})$ be the hazard of the outcome d at baseline age a among those at exposure level e with a fixed covariate vector $\mathbf{c} = (c_1, \dots, c_k)$. Suppose also that one is interested in two fixed exposure levels in particular, say e_0 and e_1 . For any given baseline age a_1 , the idea behind the RAP is to seek the earliest age a_0 such that:

$$h(a_0, e_0, \mathbf{c}) = h(a_1, e_1, \mathbf{c}). \quad (2.17)$$

If an a_0 satisfying the preceding equation exists, one can define the difference in baseline ages $a_0 - a_1$ as the RAP among e_1 -exposed as compared with e_0 -exposed, starting from the baseline age a_1 . The existence of a unique value a_0 (and therefore the uniqueness of RAP) is guaranteed by the assumption that the hazard function of d increases monotonically with age, given e and \mathbf{c} .

For example, if RAP is equal to 20 years starting from a baseline age of 40 years, then e_1 -exposed individuals that were 40 years of age at baseline experienced the same rate of the disease than e_0 -exposed subjects who were 60 years of age at baseline.

¹²To be consistent with the previous sections, the notation used in this thesis is slightly different from that used in Paper III.

¹³<http://www.chancesfp7.eu>

The form of risk and rate advancement periods under PH models

RAP can be estimated parametrically directly from PH models. In fact, by taking the logarithm of both sides of equation 2.4, one obtains:

$$\log [h(t|\mathbf{x})] = \log [h_0(t)] + \mathbf{x}^\top \boldsymbol{\beta} = \log [h_0(t)] + \beta_1 e + \beta_2 g(a) + \sum_{i=1}^k \beta_{i+2} c_i, \quad (2.18)$$

where $g(\cdot)$ is a smooth, monotonically increasing function of baseline age. The usual default transform of age is the identity function $g(a) = a$.

Under the assumptions previously introduced, a group of e_1 -exposed individuals who have a certain rate at baseline age a_1 would be expected to have reached the same rate at age a_0 , had they been e_0 -exposed, given that all the other covariates \mathbf{c} are kept constant. Therefore, according to (2.18),

$$\begin{aligned} \log [h_0(t)] + \beta_1 e_1 + \beta_2 g(a_1) + \sum_{i=1}^k \beta_{i+2} c_i &= \log [h_0(t)] + \beta_1 e_0 + \beta_2 g(a_0) + \sum_{i=1}^k \beta_{i+2} c_i \\ \beta_1 e_1 + \beta_2 g(a_1) &= \beta_1 e_0 + \beta_2 g(a_0). \end{aligned} \quad (2.19)$$

Thus, if $e_1 - e_0 = 1$, $\beta_2 \neq 0$, and $g(\cdot)$ is the identity function,

$$\text{RAP} = a_0 - a_1 = \frac{\beta_1}{\beta_2}, \quad (2.20)$$

which is the RAP for a 1-unit increase in e , expressed in the time scale of a (for example years, if baseline age is expressed in years).

Note that if $g(\cdot)$ is not the identity function, RAP is no longer constant over baseline age and it will depend on a_1 . For example, if $g(a) = \log(a)$, RAP becomes

$$\text{RAP}(a_1) = a_0 - a_1 = \left[\exp \left(\frac{\beta_1}{\beta_2} \right) - 1 \right] a_1. \quad (2.21)$$

Unfortunately, this measure has been misinterpreted in studies, commentaries, and editorials published in major epidemiologic and medical journals. Moreover, important aspects regarding RAP estimation have often been overlooked. These aspects are covered in detail in Paper III.

2.3 Dose–response meta-analysis of aggregated data

Individual epidemiologic studies on primary data usually report study findings regarding the dose–response association between a quantitative exposure and the risk of a binary disease in tabular form, as exemplified by table 2.3. The results presented in this fashion are obtained by categorizing the quantitative exposure in $J + 1$ levels, which are then modeled with indi-

cator variables keeping one exposure level as referent. The exposure-outcome association is expressed in terms of J category-specific RRs.

Generally, access to primary data for all the K studies investigating a certain exposure-disease association is not possible. As a consequence, the only way to synthesize the existing information on the overall shape of the dose-response association, and to examine whether this shape is modified by study-level characteristics, is to use aggregated (summarized) data coming from the aforementioned study-specific tables.

The common approach to dose-response meta-analysis is based on a two-stage procedure. In the first stage the dose-response associations are estimated for each of the K studies, while in the second stage the study-specific parameters defining the dose-response relations are combined using methods for multivariate meta-analysis.

2.3.1 First stage: study-specific dose-response models

Study-specific regression models

In the first stage, for each of the K studies included in the meta-analysis ($i = 1, \dots, K$), the dose-response relation between the quantitative exposure and the log-relative risks (logRRs) is estimated based on the published aggregated data (Greenland and Longnecker, 1992; Berlin et al., 1993; Orsini et al., 2006). This is done by means of the following linear model:

$$\mathbf{y}_i = \mathbf{X}_i \boldsymbol{\beta}_i + \boldsymbol{\epsilon}_i. \quad (2.22)$$

The vector \mathbf{y}_i contains the logRR estimates for all the J_i non-referent exposure categories, while \mathbf{X}_i is the $(J_i \times q)$ design matrix containing the assigned doses relative to the non-referent exposure categories and/or some flexible dose transformations. Specifically, the design matrix \mathbf{X}_i is defined as follows:

$$\mathbf{X}_i = \begin{bmatrix} g_1(x_{i1}) - g_1(x_{i0}) & \cdots & g_q(x_{i1}) - g_q(x_{i0}) \\ \vdots & & \vdots \\ g_1(x_{iJ_i}) - g_1(x_{i0}) & \cdots & g_q(x_{iJ_i}) - g_q(x_{i0}) \end{bmatrix}.$$

Table 2.3: Aggregated dose-response data for the i -th study

Exposure level	Assigned dose	Cases	n^a	RR	95% CI
0	x_{i0}	c_{i0}	n_{i0}	1	(ref)
1	x_{i1}	c_{i1}	n_{i1}	RR_{i1}	$\underline{RR}_{i1}, \overline{RR}_{i1}$
\vdots	\vdots	\vdots	\vdots	\vdots	\vdots
J_i	x_{iJ_i}	c_{iJ_i}	n_{iJ_i}	RR_{iJ_i}	$\underline{RR}_{iJ_i}, \overline{RR}_{iJ_i}$

^a Depending on the study design, this column reports person-years, total number of subjects, or number of non-cases.

For example, for a simple linear trend ($q = 1$)

$$\mathbf{X}_i = \begin{bmatrix} x_{i1} - x_{i0} \\ \vdots \\ x_{iJ_i} - x_{i0} \end{bmatrix},$$

while for a quadratic polynomial model ($q = 2$)

$$\mathbf{X}_i = \begin{bmatrix} x_{i1} - x_{i0} & x_{i1}^2 - x_{i0}^2 \\ \vdots & \vdots \\ x_{iJ_i} - x_{i0} & x_{iJ_i}^2 - x_{i0}^2 \end{bmatrix}.$$

Note that the design matrix does not include the intercept, as the logRR for the referent exposure value x_{0i} is equal to 0 (RR = 1) — that is, the regression line must pass through the origin. It is also important to underline the absence of the subscript i from the exposure transformation functions $g_1(\cdot), \dots, g_q(\cdot)$. This is because the same exposure transformations must be used for all the K studies, as it will become apparent later on, when discussing the second stage.

Lastly, β_i is a vector of unknown regression coefficients of length q , defining the study-specific dose–response association.

Approximation of the covariances between log–relative risks

The error terms ϵ_i are heteroskedastic, as the individual logRRs are not estimated with equal precision. Furthermore, a particular characteristic of model (2.22) is that the error terms are correlated, since the non-referent logRRs share a common reference group. This implies that the variance-covariance matrix of the error terms for the i -th study is equal to the following symmetric matrix

$$\text{Cov}(\epsilon_i) = \mathbf{S}_i = \begin{bmatrix} \sigma_{i11}^2 & & & & \\ \vdots & \ddots & & & \\ \sigma_{ij1} & & \sigma_{ijj}^2 & & \\ \vdots & & & \ddots & \\ \sigma_{iJ_i1} & \cdots & \sigma_{iJ_ij} & \cdots & \sigma_{iJ_iJ_i}^2 \end{bmatrix}.$$

Generally, the covariances between logRRs will be different from zero, and two different methods to approximate them using aggregated data only have been proposed (Greenland and Longnecker, 1992; Hamling et al., 2008). These methods require information about the number of cases and, depending on the study design, person-years/number of subjects/number of non-cases for each exposure level. An empirical evaluation of these approximations and a comparison between their underlying assumptions have been presented by Orsini et al. (2012). Lastly, the variances on the diagonal can be easily back calculated from the 95% CIs for the

RRs as

$$\sigma_{ijj}^2 = \left[\frac{\log(\overline{\text{RR}}_{ij}) - \log(\text{RR}_{ij})}{2 \times 1.96} \right]^2.$$

Estimation

The matrix \mathbf{S}_i , which is treated as known, is used to efficiently estimate the coefficient vector $\boldsymbol{\beta}_i$ and its variance-covariance matrix $\mathbf{V}(\boldsymbol{\beta}_i)$ using the Generalized Least Squares (GLS) estimator:

$$\hat{\boldsymbol{\beta}}_i = (\mathbf{X}_i^\top \mathbf{S}_i^{-1} \mathbf{X}_i)^{-1} \mathbf{X}_i^\top \mathbf{S}_i^{-1} \mathbf{y}_i$$

$$\hat{\mathbf{V}}(\boldsymbol{\beta}_i) = (\mathbf{X}_i^\top \mathbf{S}_i^{-1} \mathbf{X}_i)^{-1}.$$

If one assumes independence between the logRRs, the off-diagonal elements of \mathbf{S}_i are set to 0, and the Weighted Least Square (WLS) estimator is used to estimate $\boldsymbol{\beta}_i$ and $\mathbf{V}(\boldsymbol{\beta}_i)$.

Example of differences in results using primary data, WLS, and GLS

An example of the possible consequences related to ignoring the covariance between logRRs is illustrated next.

The aggregated data presented in table 2.4 is based on the analysis of actual primary data, where the association between a certain quantitative exposure and the IR of a disease was investigated. The Incidence Rate Ratio (IRR) for every 1-unit increase in the exposure was 0.918 (95% CI: 0.868–0.971), as estimated from primary data. This is the linear trend that one would like to “reconstruct” using only summarized data.

Setting the off-diagonal elements of \mathbf{S} equal to 0, the IRR estimated from aggregated data using WLS was equal to 1.066 (95% CI: 1.000–1.135), wrongly identifying the direction of the association. On the other hand, the IRR estimated approximating the covariances and employing the GLS estimator was 0.922 (95% CI: 0.865–0.983), very close to the IRR calculated from primary data.

Table 2.4: Example data in aggregated form as reported by a single study

Exposure category	Assigned dose ^a	Cases	Person-years	IRR	95% CI
< 4.2	4.0	128	21,937	1.00	(ref)
4.2–4.6	4.4	463	63,153	1.26	1.03–1.53
4.6–5.0	4.8	838	118,327	1.21	1.01–1.46
5.0–5.5	5.2	973	139,864	1.19	0.99–1.43
5.5–6.0	5.7	456	69,412	1.12	0.92–1.37
≥ 6.0	6.3	244	43,629	0.96	0.77–1.19

^a The reported assigned doses are the category-specific median values calculated from primary data.

2.3.2 Second stage: multivariate meta-analysis

In the second stage, the estimated vectors of study-specific regression coefficients are pooled using methods for multivariate meta-analysis (Berkey et al., 1998; van Houwelingen et al., 2002; Jackson et al., 2010, 2011; Gasparrini et al., 2012).¹⁴

The multivariate model

The result of the first stage is a set of K vectors of regression coefficients $\hat{\beta}_i$ of length q , and the relative ($q \times q$) estimated variance-covariance matrices $\hat{V}(\beta_i)$. The vectors $\hat{\beta}_i$ are now used as outcomes in a random-effect multivariate meta-analysis model

$$\hat{\beta}_i \sim N_q(\theta, \hat{V}(\beta_i) + \Psi). \quad (2.23)$$

The marginal model shown in (2.23) has independent within- ($\hat{V}(\beta_i)$) and between-study components (Ψ), with $\hat{V}(\beta_i) + \Psi = \Sigma_i$. In particular, in the within-study component, the estimated $\hat{\beta}_i$ is assumed to be sampled with error from $N_q(\beta_i, V(\beta_i))$ — that is, a q -variate normal distribution where β_i is the vector of true unknown dose–response coefficients for the i -th study. On the other hand, in the between-study component, β_i is assumed sampled from $N_q(\theta, \Psi)$, where Ψ is the unknown ($q \times q$) between-study variance-covariance matrix. The vector θ can be interpreted as the population-average outcome parameters, which are the coefficients defining the population-average dose–response relation.

Some considerations regarding model (2.23) can be made. First, in contrast to the setting where multivariate meta-analysis is used to analyze diagnostic test accuracy or multiple outcomes simultaneously (Arends et al., 2003), in the present setting it is not necessary for the model parameters to be individually interpretable, rather the pooled dose–response association is described by their joint distribution. Second, if $q = 1$ the model reduces to a univariate random-effect meta-analytical model. Third, assuming that $\Sigma_i = V(\beta_i)$ — that is, no between-study variability — the model becomes a fixed-effect model.

Multivariate meta-regression

When the shape of the dose–response association differs according to study-level covariates (for example, study location or study design), model (2.23) can be extended to multivariate meta-regression (van Houwelingen et al., 2002; Gasparrini et al., 2012). This means that the q outcomes of the second stage are modeled in terms of m study-level covariates $\mathbf{z}_i = (z_{i1}, \dots, z_{im})$ (generally including an intercept) associated with the i -th study

$$\hat{\beta}_i \sim N_q(\mathbf{Z}_i \theta, \hat{V}(\beta_i) + \Psi). \quad (2.24)$$

The matrix \mathbf{Z}_i is a ($q \times qm$) block-diagonal matrix of full rank and is derived by taking the

¹⁴Multivariate random-effect meta-analysis was first introduced by van Houwelingen, Zwinderman, and Stijnen (1993).

Kronecker product between an identity matrix of dimension q ($\mathbf{I}_{(q)}$) and the vector \mathbf{z}_i , such that

$$\mathbf{Z}_i = \mathbf{I}_{(q)} \otimes \mathbf{z}_i^\top = \begin{bmatrix} 1 & z_{i2} & \cdots & z_{im} & \cdots & 0 & 0 & \cdots & 0 \\ \vdots & & & & \ddots & & & & \\ 0 & 0 & \cdots & 0 & \cdots & 1 & z_{i2} & \cdots & z_{im} \end{bmatrix},$$

where $z_{i1} = 1$ is the intercept term. For example, suppose that the dose–response association is modeled using a quadratic polynomial ($q = 2$) and that the only study-covariate of interest is a binary variable indicating whether the i -th study was conducted in Sweden [$\mathbf{z}_i = (1, 1)$] or not [$\mathbf{z}_i = (1, 0)$]. The matrix \mathbf{Z}_i for a study conducted in Sweden is therefore

$$\mathbf{Z}_i = \mathbf{I}_{(2)} \otimes \mathbf{z}_i^\top = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} \otimes (1, 1) = \begin{bmatrix} 1 & 1 & 0 & 0 \\ 0 & 0 & 1 & 1 \end{bmatrix},$$

while for a study conducted elsewhere it is

$$\mathbf{Z}_i = \mathbf{I}_{(2)} \otimes \mathbf{z}_i^\top = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} \otimes (1, 0) = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 \end{bmatrix}.$$

The coefficient vector $\boldsymbol{\theta}$ is now of length qm and defines the association between the q outcomes and the m study-level covariates. The q coefficients in $\boldsymbol{\theta}$ related to the intercept terms are interpreted as the population-average outcome parameters for those studies characterized by a zero value of study-level covariates. The remaining $(qm - q)$ coefficients express how the population-average outcome parameters vary in respect to the values taken by the study-level covariates.

Estimation

Different estimation methods have been proposed for random-effect multivariate meta-analysis, including likelihood-based methods and method of moments. The goal is to estimate the qm model parameters $\boldsymbol{\theta}$ and the parameters $\boldsymbol{\psi}$ of the between-study variance-covariance matrix $\boldsymbol{\Psi}$ [$q(q + 1)/2$ parameters if no structure for $\boldsymbol{\Psi}$ is assumed].

ML estimates of $\boldsymbol{\theta}$ and $\boldsymbol{\psi}$ can be obtained simultaneously by numerically maximizing the log-likelihood function of the marginal model (2.24), subject to the constraint that $\boldsymbol{\Psi}$ is positive semi-definite (White, 2011). Under the common assumption that the K studies are independent, the log-likelihood function is proportional to the logarithm of the product of K q -variate normal densities:

$$l(\boldsymbol{\theta}, \boldsymbol{\psi}; \hat{\boldsymbol{\beta}}_i, \hat{\mathbf{V}}(\boldsymbol{\beta}_i), \mathbf{Z}_i) = -\frac{1}{2} \sum_{i=1}^K \log |\boldsymbol{\Sigma}_i| - \frac{1}{2} \sum_{i=1}^K \left[(\hat{\boldsymbol{\beta}}_i - \mathbf{Z}_i \boldsymbol{\theta})^\top \boldsymbol{\Sigma}_i^{-1} (\hat{\boldsymbol{\beta}}_i - \mathbf{Z}_i \boldsymbol{\theta}) \right]. \quad (2.25)$$

Assuming that the elements of $\boldsymbol{\Psi}$ are known, the parameter vector $\boldsymbol{\theta}$ and its accompanying variance-covariance matrix $\mathbf{V}(\boldsymbol{\theta})$ can be estimated, conditional on $\boldsymbol{\psi}$, by maximizing (2.25).

In this case, closed-form equations are given by the GLS estimator

$$\hat{\boldsymbol{\theta}} = \left(\sum_{i=1}^K \mathbf{z}_i^\top \hat{\mathbf{V}}(\boldsymbol{\beta}_i)^{-1} \mathbf{z}_i \right)^{-1} \sum_{i=1}^K \mathbf{z}_i^\top \hat{\mathbf{V}}(\boldsymbol{\beta}_i)^{-1} \hat{\boldsymbol{\beta}}_i \quad (2.26)$$

$$\hat{\mathbf{V}}(\boldsymbol{\theta}) = \left(\sum_{i=1}^K \mathbf{z}_i^\top \hat{\mathbf{V}}(\boldsymbol{\beta}_i)^{-1} \mathbf{z}_i \right)^{-1}. \quad (2.27)$$

To avoid the downward bias of ML estimates of $\boldsymbol{\psi}$, the parameters of the between-study variance-covariance matrix can be estimated using Restricted Maximum Likelihood (REML) (White, 2011). This bias is due to the fact that ML does not account for the loss of degrees of freedom from the estimation of $\boldsymbol{\theta}$. REML estimation is carried out by iteratively maximizing the following restricted log-likelihood, which is a function of $\boldsymbol{\psi}$ only and is proportional to:

$$l_{\text{REML}}(\boldsymbol{\psi}; \hat{\boldsymbol{\beta}}_i, \hat{\mathbf{V}}(\boldsymbol{\beta}_i), \mathbf{z}_i, \hat{\boldsymbol{\theta}}) = -\frac{1}{2} \sum_{i=1}^K \log |\boldsymbol{\Sigma}_i| - \frac{1}{2} \log \left| \sum_{i=1}^K \mathbf{z}_i^\top \boldsymbol{\Sigma}_i^{-1} \mathbf{z}_i \right| - \frac{1}{2} \sum_{i=1}^K \left[(\hat{\boldsymbol{\beta}}_i - \mathbf{z}_i \hat{\boldsymbol{\theta}})^\top \boldsymbol{\Sigma}_i^{-1} (\hat{\boldsymbol{\beta}}_i - \mathbf{z}_i \hat{\boldsymbol{\theta}}) \right],$$

where $\hat{\boldsymbol{\theta}}$ is obtained from (2.26).

Lastly, a less computationally intensive method for multivariate meta-analysis is based on the extension of the univariate method of moments proposed by DerSimonian and Laird (1986) to the multivariate scenario (Jackson et al., 2010). Moreover, since the estimating procedure for the parameters of $\boldsymbol{\Psi}$ is based on moments arguments only, the assumption of between-study normality is not necessary.

Note that if one assumes that $\boldsymbol{\Sigma}_i = \mathbf{V}(\boldsymbol{\beta}_i)$, the parameter vector $\boldsymbol{\theta}$ and its variance-covariance matrix $\mathbf{V}(\boldsymbol{\theta})$ can be estimated using (2.26) and (2.27), respectively.

Between-study heterogeneity

Meta-regression can be employed to identify sources of variation in study findings and for this reason it can help explaining heterogeneity in the dose-response associations across studies. The hypothesis of no heterogeneity between studies beyond that explained by sampling variability and study-level covariates can be tested by means of the multivariate extension of the Cochran Q test (Ritz et al., 2008; Jackson et al., 2012). Formally, the null hypothesis is $H_0 : \boldsymbol{\Psi} = \mathbf{0}$ and the test statistic is defined as

$$Q = \sum_{i=1}^K \left[(\hat{\boldsymbol{\beta}}_i - \mathbf{z}_i \hat{\boldsymbol{\theta}})^\top \hat{\mathbf{V}}(\boldsymbol{\beta}_i)^{-1} (\hat{\boldsymbol{\beta}}_i - \mathbf{z}_i \hat{\boldsymbol{\theta}}) \right], \quad (2.28)$$

where $\hat{\boldsymbol{\theta}}$ is estimated using a fixed-effect model. Under the null hypothesis, the Q follows asymptotically a chi-square distribution with $(Kq - qm)$ degrees of freedom. This statistic reduces to the classic Q statistic if $q = 1$ (Cochran, 1954).

Furthermore, the multivariate extension of the I^2 statistic proposed by Jackson et al. (2012) can be used to measure the percentage of total variability attributable to between-study heterogeneity, analogously to the univariate case (Higgins and Thompson, 2002). The I^2 index is defined as

$$I^2 = \max\left(0, \frac{Q - (Km - qm)}{Q}\right) \times 100\%. \quad (2.29)$$

Both the Q test and the I^2 index have some limitations. The Q test, in particular, has been shown to suffer from low power when the number of studies is small or the “total information” is limited (Hardy and Thompson, 1998). On the other hand, the I^2 has been criticized for being dependent on precision of the estimates from the first-stage regression models (Rücker et al., 2008).

Prediction of the population-average dose–response association

The prediction of the population-average dose–response association is a crucial step to display the results in tabular and in graphical form. In particular, the goal is to present how the risk of the disease varies according to levels of the quantitative exposure, choosing a particular exposure value as the referent (for example, a specific BMI value or no alcohol consumption). Moreover, in the presence of study-level covariates, one is interested in showing how they modify the overall dose–response association.

Let \mathbf{X} be the $(v \times q)$ first-stage design matrix evaluated at an arbitrary number v of exposure doses, and let \mathbf{X}_{ref} be the same design matrix evaluated at the chosen reference level. Furthermore, let \mathbf{z} be the $(m \times 1)$ vector containing the study-level covariates fixed at a particular level. The $(v \times 1)$ vector of predicted RRs conditional on a certain study-level covariate pattern is given by

$$\widehat{\mathbf{RR}}_{v \times 1} = \exp \left[\begin{pmatrix} \mathbf{X} & -\mathbf{X}_{\text{ref}} \\ v \times q & v \times q \end{pmatrix} \begin{pmatrix} \mathbf{I}_{(q)} \otimes \mathbf{z}^\top \\ q \times qm \end{pmatrix} \hat{\boldsymbol{\theta}}_{qm \times 1} \right].$$

The $100(1 - \alpha)\%$ confidence interval for the predicted pooled dose–response curve is obtained as

$$\exp \left\{ \log(\widehat{\mathbf{RR}}) \pm z_{1-\frac{\alpha}{2}} \text{diag} \left[((\mathbf{X} - \mathbf{X}_{\text{ref}}) \mathbf{Z}) \hat{\mathbf{V}}(\boldsymbol{\theta}) ((\mathbf{X} - \mathbf{X}_{\text{ref}}) \mathbf{Z})^\top \right]^{\frac{1}{2}} \right\},$$

where $\hat{\mathbf{V}}(\boldsymbol{\theta})$ is the $(qm \times qm)$ estimated variance-covariance matrix relative to $\hat{\boldsymbol{\theta}}$, and $z_{1-\alpha/2}$ is the $(1 - \alpha/2)$ quantile of a standard normal distribution.

Goodness of fit

The last step of a dose–response meta-analysis should be the evaluation of its goodness of fit. However, despite the importance of assessing whether the posited dose–response models provide an adequate description of the available aggregated data, this is rarely, if ever, done in practice. Paper V will present 3 tools to evaluate the goodness of fit of a dose–response meta-analysis, while taking into account the correlation among the logRRs.

Chapter 3

Aims of the thesis

The overall aims of this thesis were to investigate the association between BMI and prostate cancer incidence and mortality, and to address specific methodological issues related to the analysis of primary and aggregated data.

More specifically, the aims were:

- To assess the association between BMI during middle-late adulthood and during early adulthood and localized/advanced prostate cancer incidence and mortality in a population-based cohort of Swedish men.
- To summarize the existing epidemiologic evidence on the association between BMI during middle-late adulthood and the incidence of prostate cancer by subtype of the disease.
- To extend the use of quantile regression for censored data, and in particular of Laplace regression, to those situations where the time scale of interest is attained age at the event instead of follow-up time.
- To discuss how RAP has been misinterpreted in the epidemiologic literature and to show how RAP is profoundly sensitive to the specification of disease dependence on age.
- To present and discuss relevant methods to evaluate the goodness of fit of dose–response meta-analyses of binary outcomes.

Chapter 4

Materials and methods

Paper I and the additional results for Paper II presented in this thesis are based on the population-based longitudinal COSM study. The meta-analysis in Paper IV is based on aggregated data extracted from studies identified through a search of computerized databases, and by reviewing reference lists.

4.1 The Cohort of Swedish Men

The principal aim of the COSM¹⁵ is to investigate the relations between a number of lifestyle and diet factors and the incidence of several chronic diseases, including cancer (Harris et al., 2013).

The population-based COSM was established in the fall 1997, when all men born between 1918 and 1952 residing in Västmanland and Örebro counties in central Sweden ($n = 100303$) received an invitation to participate in the study, along with a self-administered questionnaire. This questionnaire included questions about height, current body weight, body weight across the life course (at ages 20, 30, 40, 50, 60, and 70), education, physical activity (at ages 15, 30, 50, and current), smoking habits, family history of prostate cancer, and diet.

A total of 48,850 men returned the questionnaire (49%). After excluding those participants who reported an incorrect/incomplete personal identification number ($n = 205$),¹⁶ returned an incomplete questionnaire ($n = 92$), died before 1 January 1998 ($n = 55$), or had a prevalent cancer diagnosis (except non-melanoma skin cancer) ($n = 2592$), the final cohort consisted of 45,906 men. The follow-up period started the 1st of January 1998.

The COSM is comparable to the general Swedish population of men aged 45–79 years in 1997 with regards to age distribution, education level, and proportion of overweight ($\text{BMI} > 25 \text{ kg} \times \text{m}^{-2}$) (see table 4.1, reproduced from Harris et al., 2013).

The protocol of this study has been approved by the relevant ethical committee. All subjects gave full informed consent to participate in this study.

¹⁵<https://clinicaltrials.gov/ct2/show/NCT01127711>

¹⁶The number of men who returned the questionnaire reported in Paper I is equal to $48645 = 48850 - 205$.

Table 4.1: Comparison of the COSM with the Swedish male population aged 45–79 years in 1997, regarding age distribution, educational level, and proportion of overweight (Harris et al., 2013).

	COSM study population aged 45–79 years in 1997	Swedish male population aged 45–79 years in 1997^a
Age groups (years)		
Total (n)	45,906	1,594,952
45–49 (%)	15.9	19.5
50–54 (%)	18.8	20.8
55–59 (%)	15.9	15.6
60–64 (%)	13.1	12.5
65–69 (%)	14.1	11.6
70–74 (%)	12.4	10.8
75–79 (%)	9.9	9.2
Education, ages 48–74 years^b		
Total (n)	41,382	144,585
≤ 12 years (%)	82.3	77.1
>12 years (%)	17.3	21.0
Overweight (BMI >25 kg×m⁻²), by age groups (years)		
45–54 (%)	54.5	57.2
55–64 (%)	59.1	60.3
65–74 (%)	59.8	57.0
75–84 (%)	47.5	43.0

^a Data from SCB.

^b Educational level reported are for those ≤ 74 years of age since data from SCB were not available for older ages.

4.2 The national registers

4.2.1 The Swedish Cancer Register

The Swedish Cancer Register (SCR), maintained by the NBHW, was founded in 1958 and covers the whole population in Sweden. Epidemiologic research is one of the specific objectives of this register. The information available from the SCR includes patient data (personal identification number, age, sex, and residence), medical data (tumor site, histological type, and date of diagnosis), and follow-up data (including date and cause of death). Health care providers are obliged by law to report newly diagnosed cancers to the SCR. Completeness of this register was observed to be high (Barlow et al., 2009).

4.2.2 The National Prostate Cancer Register

From 1998 the NPCR includes all the incident cases of prostate adenocarcinomas diagnosed in Sweden. One of the primary aims of the NPCR is to provide data for clinical research. This register includes detailed information on tumor stage (according to the TNM staging system), Gleason score, and PSA serum level at diagnosis (van Hemelrijck et al., 2013). It has been estimated that, during the period 1998–2012, a total of 98% of men diagnosed with prostate

cancer registered in the SCR had also been registered in the NPCR (Tomic et al., 2015).

4.2.3 The Cause of Death Register

Starting from 1953, the NBHW maintains the Cause of Death Register (CDR). This register contains information on the date and underlying cause of death of all Swedish citizens, irrespective of whether they died in Sweden or abroad. The CDR is complete from 1 January 1969. The reliability of official cause-of-death statistics of prostate cancer patients in Sweden was observed to be reasonably high (Fall et al., 2008; Godtman et al., 2011).

Deaths whose underlying cause was attributed to prostate cancer (code 61 according to the International Classification of Diseases, 10th revision) are equally referred to in this thesis as ‘prostate cancer deaths’ or ‘fatal prostate cancer’.

4.3 Description of COSM data and comparison with Swedish national data

In this section we will describe prostate cancer incidence and mortality in the COSM and will compare the results with Swedish national data.

4.3.1 Prostate cancer incidence

Prostate cancer incidence in the COSM

To date, the most recent available data at the Unit of Nutritional Epidemiology (Institute of Environmental Medicine, Karolinksa Institutet) include information on incident prostate cancer cases from 1 January 1998 until 31 December 2012 (SCR data). Data regarding tumor stage, Gleason score, and PSA levels are available until 31 December 2011 (NPCR data).

During 15 years of follow up (1998–2012), a total of 4,213 newly diagnosed cases were identified. Figure 4.1 illustrates prostate cancer IRs by attained age and calendar year in the COSM. In particular, the solid lines are the predicted IRs from a single ‘flexible’ PH model, where attained age was modeled using Restricted Cubic Splines (RCS) with 3 knots placed at the 10th, 50th, and 90th percentiles of the distribution of uncensored times (corresponding to 61, 72, and 82 years of age) (Harrell, 2001). Moreover, the age-incidence curves were allowed to vary their shape across calendar year — that is, the IRs between calendar years were not forced to be proportional. The hollow circles represent the observed IRs by 5-year categories of attained age (45–49, 50–54, . . . , 80–84, and 85+) and calendar year (1998, . . . , 2012). Their size is proportional to the precision (inverse of the variance, assuming a Poisson distribution) of the estimate. As expected, the IRs increased steeply after 55–60 years of age, peaked around the age of 75 years, and generally declined thereafter.

As noted in section 2.1.1, prostate cancer incidence shows large geographical variation even within Sweden (Stattin et al., 2005; Jonsson et al., 2011). This could be partly due — despite a uniform, equal-access health-care system — to between-county differences in PSA-screening

uptake (Jonsson et al., 2011). Interestingly, the COSM study recruited participants from one high-incidence county (Västmanland) and one low-incidence county (Örebro) (Stattin et al., 2014). Not surprisingly, the age-adjusted prostate cancer IR was observed to be 16% higher among those men residing in Västmanland county at the time of enrollment as compared with those residing in Örebro county, marginally over the 15 years of follow-up [IRR: 1.16 (95% CI: 1.09–1.23)]. Figure A.1 in the appendix shows the model-based predicted IRs by attained age, calendar year, and county of enrollment. The ratio between directly age-standardized IRs for Västmanland versus Örebro county was observed to be around 1.21 during the period 2000–2001, based on registry data (Stattin et al., 2005, table I).

Comparison with Swedish national data

To the best of my knowledge, the only comparison between COSM and Swedish data in terms of prostate cancer incidence was carried out by Orsini (2008, section 5.4) in his PhD thesis. That analysis, which showed a remarkable good agreement between COSM and Swedish national data, was however limited to year 1998 only.

Information about the number of incident prostate cancer cases by 5-year classes of age ($a = 1, \dots, 9 = \text{“45–49”}, \dots, \text{“85+”}$) and calendar year ($c = 1998, \dots, 2012$) was available from the NBHW website ($d_{a,c}$),¹⁷ while the total number of men for the same categories was available from the SCB website ($N_{a,c}$).¹⁸ Under the assumption of constant prostate cancer incidence within age and calendar-year categories, the corresponding IRs in the Swedish male population were calculated as

$$h_{a,c}^* = -\log \left(1 - \frac{d_{a,c}}{N_{a,c} - \frac{d_{a,c}}{2}} \right).$$

Standardized Incidence Ratios (SIRs) were obtained comparing the observed number of incident prostate cancer cases in the COSM with the expected number of cases obtained by applying Swedish national rates to the COSM age and calendar-year structure (Breslow and Day, 1987, section 2.3). The overall SIR was calculated as follows:

$$\text{SIR}_{\cdot,\cdot} = \frac{\sum_{a=1}^9 \sum_{c=1998}^{2012} o_{a,c}}{\sum_{a=1}^9 \sum_{c=1998}^{2012} h_{a,c}^* t_{a,c}} = \frac{\sum_{a=1}^9 \sum_{c=1998}^{2012} o_{a,c}}{\sum_{a=1}^9 \sum_{c=1998}^{2012} e_{a,c}},$$

where $o_{a,c}$ was the number of observed cases, $t_{a,c}$ the total person-years in the COSM, and $e_{a,c}$ the number of expected cases. Marginal SIRs over attained age or calendar year were calculated by summing over the appropriate index (which, following standard notation, is replaced by a dot). Lastly, SIRs conditional on both attained age and calendar year were calculated as

¹⁷<http://www.socialstyrelsen.se/statistik/statistikdatabas/cancer/>

¹⁸http://www.scb.se/sv_/Hitta-statistik/Statistik-efter-amne/Befolkning/

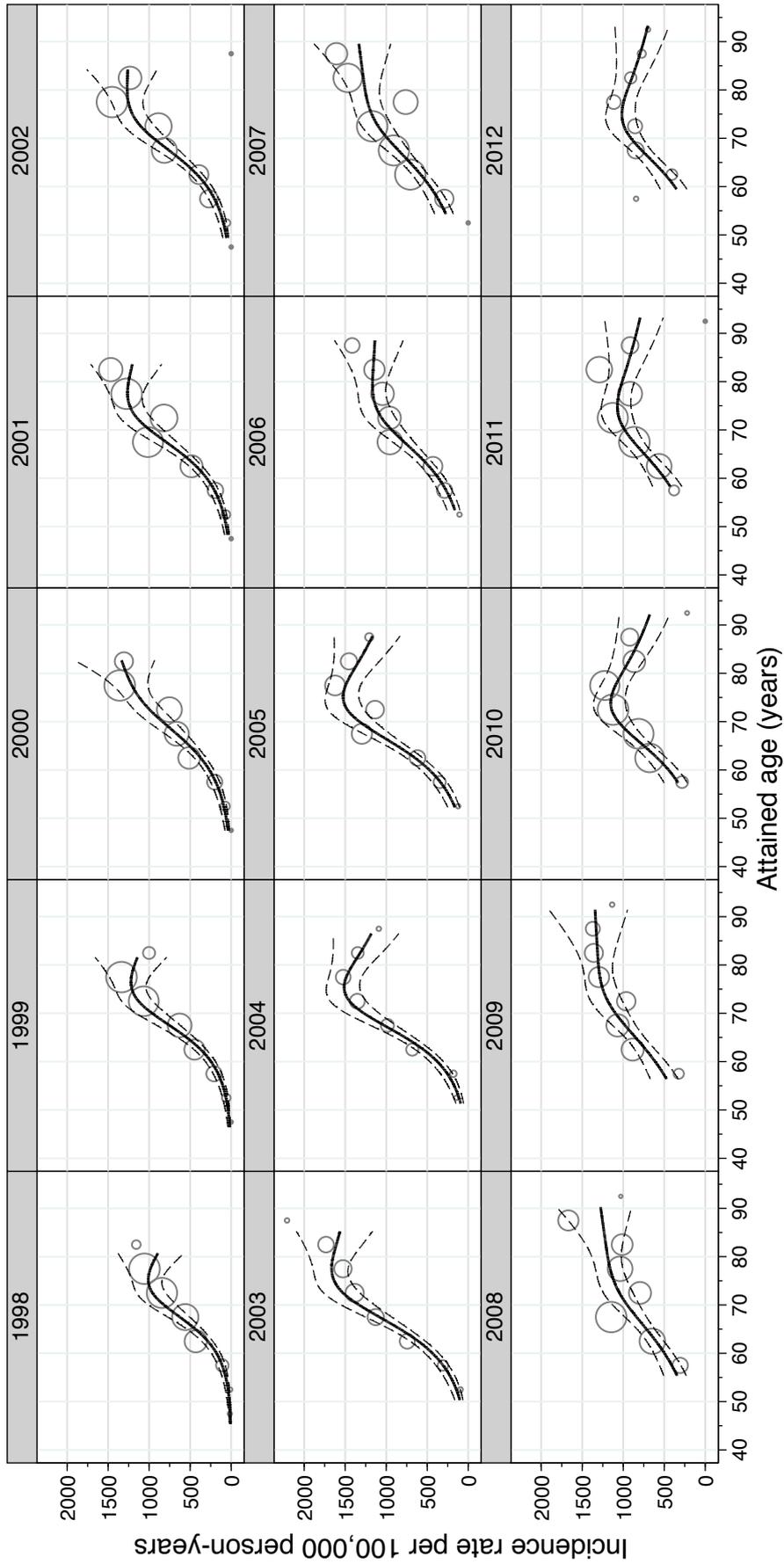


Figure 4.1: Incidence rate of prostate cancer in the COSM, conditional on calendar year and attained age. The solid line is the model-based predicted incidence rate, while dashed lines are 95% confidence intervals. The hollow circles represent the observed incidence rate by calendar year and 5-year groups of attained age. Their size is proportional to the precision (inverse of the variance) of the estimate.

$SIR_{a,c} = o_{a,c}/e_{a,c}$, for a given combination of a and c . Exact confidence intervals for the SIR can be calculated, under the assumption that the observed number of cases follows a Poisson distribution, using the formulae provided by Ulm (1990), or directly from the Poisson p.d.f. by the Newton-Raphson method. Alternatively, the number of observed cases can be modeled as a flexible function of a number of covariates (in this case, calendar year and attained age). This can be done by means of, among different methods, a multiplicative Poisson regression model — that is, a Generalized Linear Model with logarithmic link and Poisson distribution for the outcome — with an offset term containing the expected number of cases (Berry, 1983; Breslow and Day, 1987).

Table B.1 in the appendix reports the number of observed (top entry) and expected (bottom entry) prostate cancer cases according to attained age categories and calendar year in the COSM. Overall — that is, marginally over categories of attained age and calendar year — the $SIR_{.,.}$ for prostate cancer was equal to $4213/3656 = 1.15$ (95% exact CI: 1.12–1.19).

Figure 4.2 shows the observed SIRs (hollow circles) calculated marginally over categories of attained age (panel A), and over calendar year (panel B). Furthermore, in panel A, SIR was modeled as a function of calendar year using RCS with 4 knots at years 1999, 2003, 2007, and 2012 (solid line). Similarly, panel B exhibits SIR modeled as a function of attained age using RCS with 4 knots at ages 55, 65, 75 and 80 years (solid line).

There was no evidence of an association between calendar year and SIR in the RCS model ($p_{\text{overall}} = 0.21$) or in a simpler linear model ($p_{\text{linear}} = 0.88$). Note how the SIR relative to 1998 was very close to 1 [$SIR_{.,1998} = 168/173 = 1.03$ (95% exact CI: 0.88–1.19), see table B.1], in line with what observed by Orsini (2008). Conversely, attained age was observed to be associated with SIR in the RCS model ($p_{\text{overall}} < 0.001$), with evidence of non-linearity ($p_{\text{non-linearity}} = 0.002$), indicating evidence of an increased SIR at older ages as compared with younger ages.

Lastly, the SIR calculated only among those men enrolled in Västmanland county was equal to $2223/1792 = 1.24$ (95% exact CI: 1.19–1.29), while it was $1990/1865 = 1.07$ (95% exact CI: 1.02–1.11) for those men enrolled in Örebro county ($p_{\text{heterogeneity}} < 0.001$).

4.3.2 Prostate cancer mortality

Prostate cancer mortality in the COSM

Between 1 January 1998 and 31 December 2012, a total of 691 deaths whose underlying cause was attributed to prostate cancer were observed in the COSM (CDR data). Figure 4.3 shows prostate cancer MRs by attained age and calendar year. The solid lines are the model-based MRs from a ‘flexible’ PH regression model, where attained age was modeled using RCS with 3 knots at 67, 80, and 87 years of age. The PH assumption was once again relaxed via time-dependent coefficients for calendar year.

The interpretation of the analysis on prostate cancer mortality is affected by the fact that the COSM is a cohort of cancer-free men at baseline. In fact, as described previously, all men with a prevalent cancer diagnosis at baseline were excluded from the study. It is therefore not

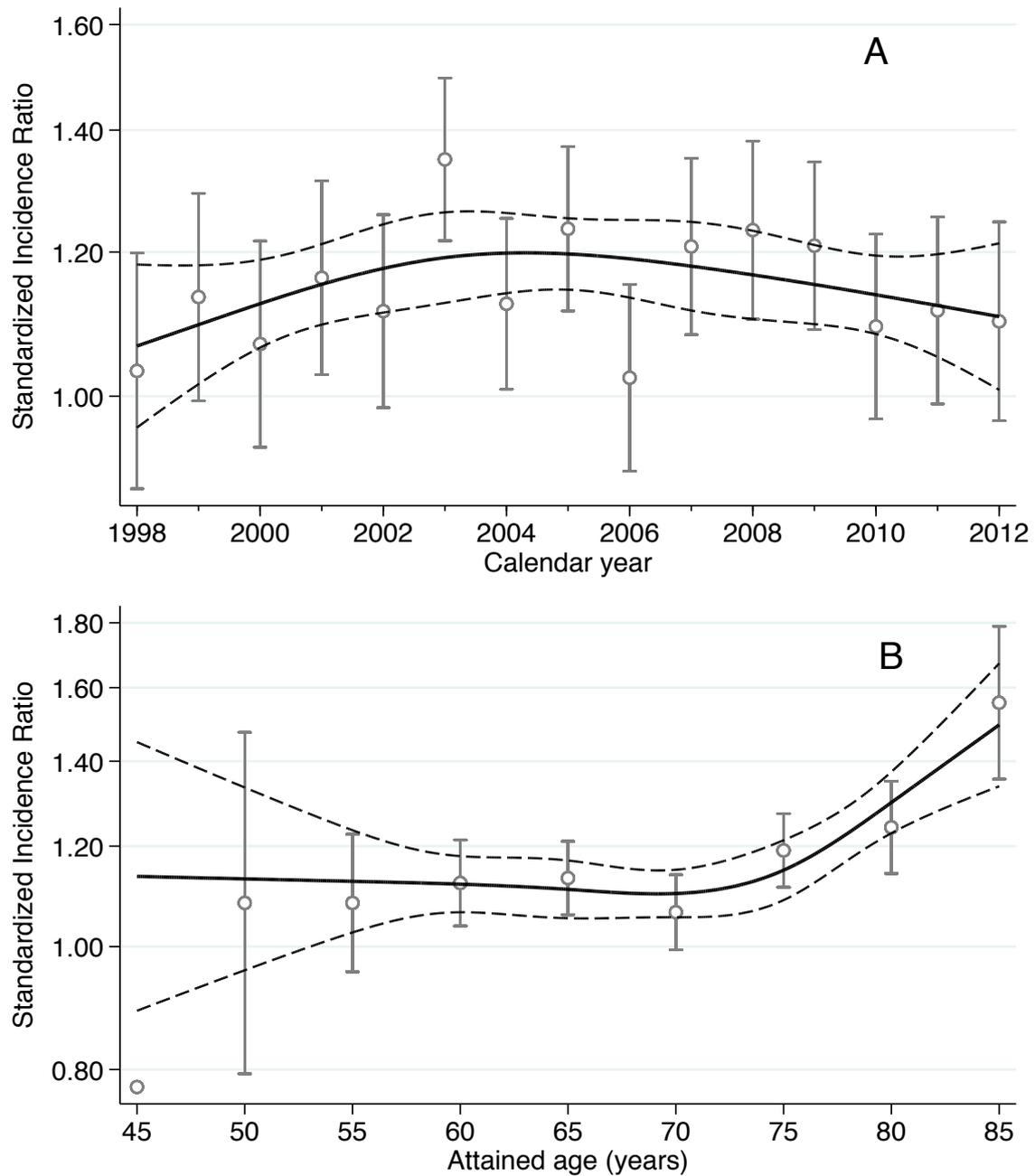


Figure 4.2: SIRs of prostate cancer by calendar year (panel A) and attained age (panel B). The solid lines are model-based predicted SIRs, while dashed lines are 95% confidence intervals. The hollow circles represent the observed SIRs by 5-year groups of attained age and calendar year together with 95% confidence intervals. The confidence interval for $SIR_{1.}$ was not displayed since extremely wide, as it was based on 1 case only (see table B.1). The vertical axes are on the natural log scale.

surprising that the prostate cancer MRs were very low during the first years of follow-up, even at older ages. For example, in 1998 only 2 deaths due to prostate cancer were observed. On the other hand, during the last years of follow-up, the mortality curves showed a very steep increase at older ages, in line with what one would expect.

Over the 15 years of follow-up, the MR was shown to be 9% lower among those men residing in Västmanland county at baseline as compared with those men residing in Örebro county [Mortality Rate Ratio (MRR): 0.91 (95% CI: 0.78–1.06)]. Similarly, restricting the analysis to the last 6 years of follow-up (2007–2012, 406 prostate cancer deaths), the MRR was observed to be 0.88 (95% CI: 0.72–1.07).

The lower prostate cancer-specific mortality¹⁹ observed in Sweden by Stattin et al. (2014) in high-incidence counties as compared with low-incidence counties, among men aged 50–74 years and during the years 2000–2009 [RR: 0.87 (95% CI: 0.81–0.95)], was similar to that observed between Västmanland and Örebro counties in the COSM [prostate cancer-specific MRR: 0.85 (95% CI: 0.73–0.99)].

Comparison with Swedish national data

Comparison of prostate cancer MRs between COSM and Swedish national data was carried out in terms of Standardized Mortality Ratios (SMRs). Source of Swedish data, statistical tools, and notation are identical to those described in section 4.3.1.

Table B.2 reports the number of observed (top entry) and expected (bottom entry) prostate cancer deaths in the COSM according to attained age categories and calendar year. Overall, $SMR_{.,.} = 691/1034 = 0.67$, with 95% exact CI equal to 0.62–0.72. Again, this is not surprising given that the comparison was made between two populations, one of which was cancer-free at baseline while the other one was not.

Figure 4.4 shows the observed SMRs by calendar year calculated marginally over categories of attained age (hollow circles), as well as the SMR modeled as a function of calendar year using RCS with 4 knots positioned at years 1998, 2002, 2007, and 2012 (solid line). In the RCS model, there was evidence of an association between calendar year and SMR ($p_{\text{overall}} < 0.001$) and also of non-linearity ($p_{\text{non-linearity}} < 0.001$). The observed SMRs were as low as 0.05 in 1998 [$SMR_{.,1998} = 2/43 = 0.05$ (95% exact CI: 0.01–0.17)], and increased over calendar year to level off after, say, year 2004/2005, not far from the value of 1. At the same time, no systematic variation in SMR was observed when modeled as a function of attained age (figure A.2).

One might have expected a longer time period before the SMRs approached values closer to 1, given the long latency of prostate cancer. However, the COSM was ‘cancer-free at baseline’ only in the sense that those men with a prevalent cancer diagnosis were excluded. Therefore, men with an undiagnosed prostate cancer were still included in the cohort. This can have contributed to a relatively shorter period before the prostate cancer MRs in the COSM reached

¹⁹Prostate cancer-specific mortality refers to mortality due to prostate cancer among men diagnosed with the disease.

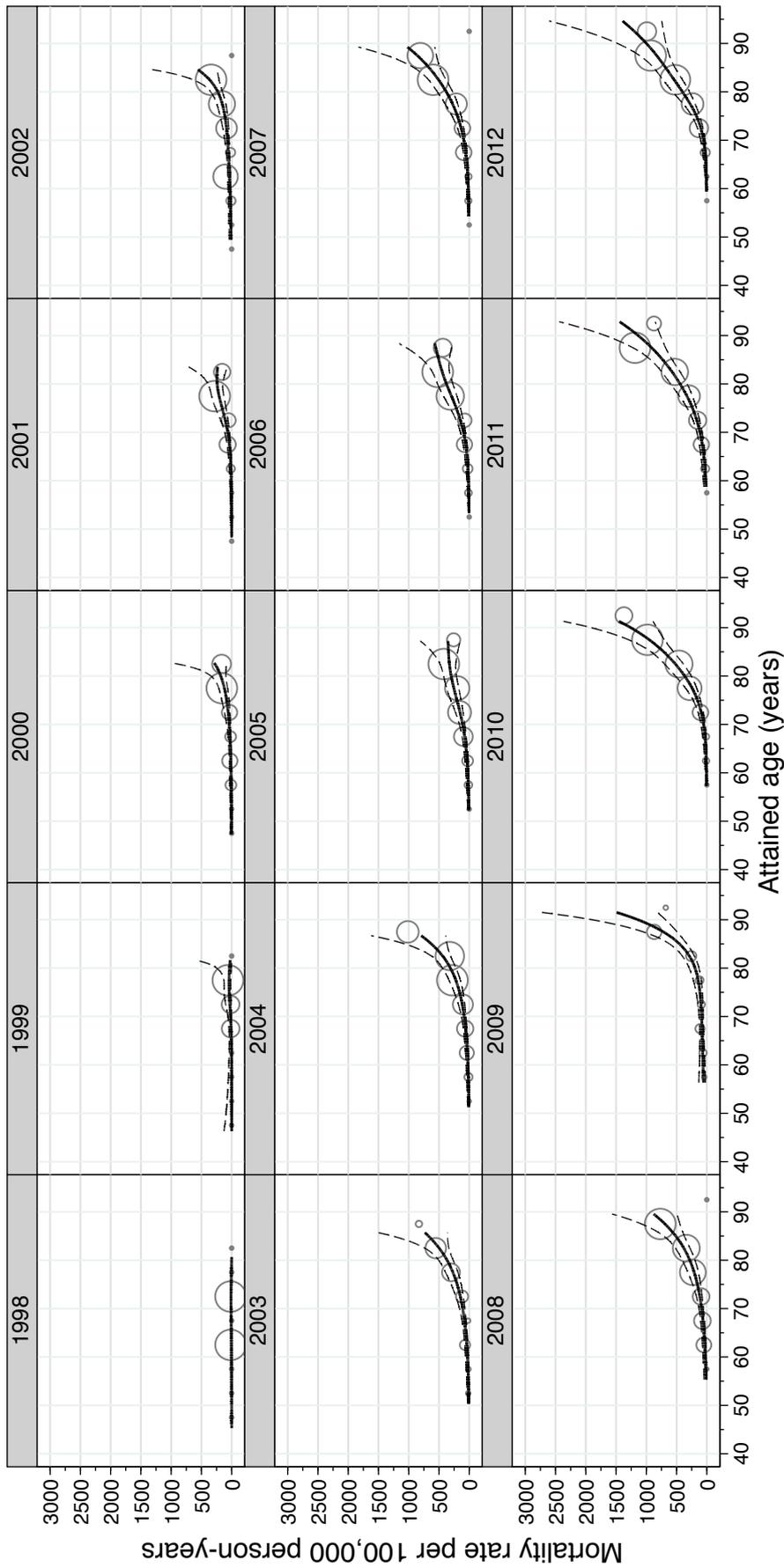


Figure 4-3: Prostate cancer mortality rates in the COSM, conditional on calendar year and attained age. The solid line is the model-based predicted incidence rate, while dashed lines are 95% confidence intervals. Note that the confidence interval for year 1998 is not displayed due to only 2 prostate cancer deaths during the whole year. The hollow circles represent the observed incidence rate by calendar year and 5-year groups of attained age. Their size is proportional to the precision (inverse of the variance) of the estimate.

comparable levels to those observed in Sweden.

Lastly, considering the years 2006–2012 only, there was no evidence that the SMR for those men enrolled in Västmanland county [$\text{SMR}_{,2006-2012} = 210/278 = 0.75$ (95% exact CI: 0.66–0.86)] was different from that for those men enrolled in Örebro county [$\text{SMR}_{,2006-2012} = 251/289 = 0.87$ (95% exact CI: 0.76–0.98)] ($p_{\text{heterogeneity}} = 0.14$).

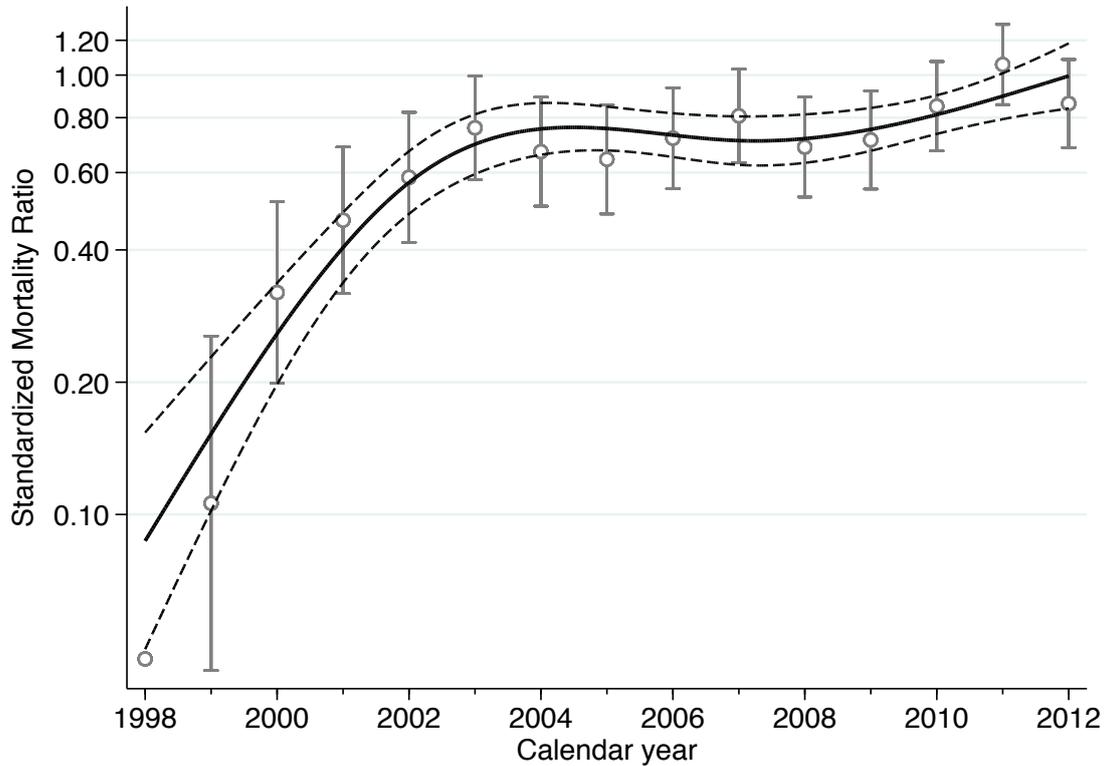


Figure 4.4: SMRs of prostate cancer by calendar year. The solid line is the model-based predicted SMR, while dashed lines are 95% confidence intervals. The hollow circles represent the observed SMRs by calendar year together with 95% confidence intervals. The confidence interval for $\text{SIR}_{,1998}$ was not displayed since extremely wide, as it was based on 2 deaths only (table B.2). The vertical axis is on the natural log scale.

4.4 Paper I

Exposure assessment

BMI during early adulthood was calculated as recalled weight (in kilograms) at the age of 30 years multiplied by self-reported height (in meters) to the power of minus 2. In a similar fashion, BMI during middle-late adulthood was computed from the self-reported weight at baseline — that is, at ages 45–79 years — and self-reported height. In addition to the exclusions described in section 4.1, we excluded those men with BMI at baseline or at 30 years of age outside the range $15\text{--}40 \text{ kg}\times\text{m}^{-2}$ ($n = 196$) or missing ($n = 8751$), leaving thus 36,959 men for the analyses.

Outcome assessment

Incident cases of prostate cancer were ascertained by linkage with the SCR, while linkage with the NPCR provided data regarding TNM staging, Gleason score, and PSA serum level at diagnosis. Prostate cancer cases were classified by subtype of the disease either as localized [T1–2 and Nx–0 and (Mx–0 or PSA < 20 ng×ml⁻¹ or Gleason score 2–7)] or advanced [T3–4 and Nx–1 and (Mx–1 or PSA > 100 ng×ml⁻¹ or Gleason score 8–10)]. These classification criteria do not exactly match with those used by the NPCR (2013). Nevertheless, the definition of localized cases is comparable to the combination of ‘low-risk’ and ‘intermediate-risk’ categories, whereas the definition of advanced cases is comparable to the combination of ‘regionally metastatic’ and ‘distant metastases’ categories (table 2.1). Information on prostate cancer deaths was obtained from the CDR.

From 1 January 1998 to 31 December 2008, during 371,792 person-years, a total of 1,530 localized and 554 advanced cases were identified. From 1 January 1998 to 31 December 2007, during 333,702 person-years, 225 cases of prostate cancer death were documented.

Statistical analysis

Cox PH models were used to examine the multivariable-adjusted association of both BMI at 30 years of age and BMI at baseline age with the IR or MR of prostate cancer, as appropriate. The exposures were modeled as continuous variables and second-degree Fractional Polynomials (FP2) (Royston et al., 1999) were employed whenever this provided a better overall fit of the model, as measured by the Akaike Information Criterion (AIC). The value of 22 kg×m⁻² was used as the referent. Models were adjusted for age (years), total energy intake (kcal), total physical activity (<37.9, 38.0–40.9, 41.0–44.9, ≥45.0 MET-h/day), education (years), smoking status (current, former, never smoker), family history of prostate cancer (yes, no, don't know), and personal history of diabetes (yes, no).

Updated analysis

In section 5.1.2, we present updated analyses using the most recent data available at our Unit to take advantage of the extended follow-up period.

The number of subjects in the study ($n = 36959$) and the classification criteria for localized and advanced subtypes of prostate cancer were left unchanged. The follow-up was extended until 31 December 2011 for incidence of prostate cancer subtypes, and until 31 December 2012 for prostate cancer mortality. During 456,322 person-years, a total of 2,078 localized cases and 727 advanced cases were identified. On the other hand, during 500,765 person-years, 508 deaths attributed to prostate cancer were documented.

Multivariable-adjusted Cox PH models, similar to those previously described, were employed. In these updated analyses, however, the baseline hazard was allowed to vary between counties of residence at baseline (Västmanland/Örebro) by means of stratified Cox models (van Houwelingen and Stijnen, 2013). Results were presented in tabular form by categorizing

BMI in 6 groups: < 21.0, 21.0–22.9 (referent), 23.0–24.9, 25.0–27.4, 27.5–29.9, and ≥ 30.0 $\text{kg}\times\text{m}^{-2}$.

In the analysis on localized prostate cancer, BMI at baseline age was again modeled using FP2. Moreover, RCS with 4 knots placed at the 5th, 35th, 65th, and 95th percentiles of the distributions of BMI at baseline age and of BMI at age 30 years were also employed for all the analyses.²⁰ Lastly, we examined whether the associations differed according to county of residence at baseline by including appropriate product terms in the Cox models.

4.5 Paper IV

Literature search and study characteristics

Identification of the studies reporting information about the association between BMI and incidence of localized and advanced prostate cancer was done by searching the Medline (PubMed) and Embase databases. The search query was the following: (obesity or BMI or “body size” or adiposity) and “prostate cancer”. Moreover, reference lists from reviews and other relevant publications were reviewed to identify further studies to be included in the meta-analysis. Lastly, effort was put in the identification of possible studies not included in the computerized databases.

A total of 15 articles were left after the exclusion of case-control studies ($n = 54$), studies not reporting results separately by prostate cancer subtypes ($n = 16$), and duplicate studies on the same population ($n = 2$). In addition, 2 out of these 15 studies were excluded because did not report the number of cases and person-years per BMI category (Habel et al., 2000; Gong et al., 2006), which is necessary to approximate the study-specific variance-covariance matrix S_i .

Consequently, 13 prospective studies were available for the analyses (Cerhan et al., 1997; Giovannucci et al., 1997; Putnam et al., 2000; Schuurman et al., 2000; MacInnis et al., 2003; Kurahashi et al., 2006; Littman et al., 2007; Rodriguez et al., 2007; Wright et al., 2007; Pischon et al., 2008; Wallström et al., 2009; Stocks et al., 2010; Discacciati et al., 2011), 1 of which reported results only for advanced prostate cancer (Giovannucci et al., 1997), leaving thus 12 articles for the meta-analysis on localized prostate cancer. A flowchart summarizing the identification of relevant studies is shown in Paper IV, figure 1, while detailed information about the single studies is available in Paper IV, supplemental table S1.

The 12 studies on localized prostate cancer, published during the period 1997–2011, involved a total of 1,033,009 men and 19,130 incident cases. Five of these studies were conducted in the U.S., 3 in Sweden, 1 in the Netherlands, 1 in Australia, 1 in Japan, and 1 was an European multi-centre study. Four studies relied on trained personnel to collect weight and height, while the remaining 8 studies were based on self-reported measurements. Lastly, three studies provided RR estimates adjusted for both physical activity and personal history of

²⁰Corresponding to knots placed at 20.9, 24.3, 26.5, and 31.6 $\text{kg}\times\text{m}^{-2}$ for BMI at baseline age, and at 19.4, 22.1, 23.8, and 27.4 $\text{kg}\times\text{m}^{-2}$ for BMI at age 30 years.

diabetes, while 9 studies adjusted only for one of these two variables or for neither.

The 13 studies on advanced prostate cancer included a total of 1,080,790 men and 7,067 newly diagnosed cases. The study that reported results only for advanced prostate cancer was conducted in the U.S, relied on self-reported weight and height measurements, and did not adjust for physical activity or for personal history of diabetes.

Interestingly, the criteria used to classify incident prostate cancer cases as localized or advanced were very heterogeneous. In particular, they were based on the Gleason score, World Health Organization grading system, TNM and Jewett–Whitmore staging system, PSA level, or different combinations of these.

Updated dose–response meta-analysis

For localized prostate cancer, the studies by MacInnis et al. (2003) [Melbourne Collaborative Cohort Study (MCCS)] and Paper I (COSM) were superseded by Bassett et al. (2012) and by the updated analyses presented in section 5.1.2, respectively. The study by Gong et al. (2006) was included assuming 0 correlation between the logRRs. The study by Schuurman et al. (2000) was excluded because it reported only a linear trend. Lastly, 2 studies not included in Paper IV were added to the meta-analysis (Hernandez et al., 2009; Grotta et al., 2015). Thus, a total of 14 prospective cohort studies were available for the analysis, including a total of 1,081,926 and 26,500 cases.

For advanced prostate cancer, the studies by MacInnis et al. (2003) (MCCS) and Paper I (COSM) were superseded by Bassett et al. (2012) and by the analyses presented in section 5.1.2, respectively. The studies by Habel et al. (2000) and by Gong et al. (2006) were included assuming that the reported logRR estimates were uncorrelated. The study by Schuurman et al. (2000) was excluded because it reported only a linear trend. Lastly, 4 studies were added to the meta-analysis (Hernandez et al., 2009; Shafique et al., 2012; Grotta et al., 2015; Møller et al., 2015). In summary, the meta-analysis on advanced prostate cancer was based on 18 prospective studies including 1,240,222 men and 10,174 incident cases.

Chapter 5

Results

5.1 Paper I

In this paper we examined the association of BMI during early adulthood (30 years of age) and middle-late adulthood (45–79 years of age) with the incidence of prostate cancer subtypes and with prostate cancer mortality in the population-based COSM.

5.1.1 Main results

Baseline age-standardized characteristics of the study participants according to categories of BMI during middle-late adulthood are presented in Paper I, table 1. Overweight and obese men at baseline were more likely to have a personal history of diabetes and to be former smokers as compared with underweight and normal-weight men. On the other hand, they were less likely to be physically active or well-educated.

Multivariable-adjusted IRRs and MRRs according to levels of BMI at baseline age and BMI at age 30 years are presented in Paper I, table 2, table 3, and figure 1.

For localized prostate cancer, BMI at baseline age was modeled using the best-fitting FP2 transformation, which was characterized by fractional powers $(-2, -2)$. This increased the overall fit of the model as compared with modeling BMI in a linear fashion ($AIC_{FP2(-2,-2)} = 36614$ versus $AIC_{linear} = 36616$), and conferred to the relationship between BMI at baseline age and IR of localized prostate cancer an inverse-U shape. In particular, the IR of localized prostate cancer at $35 \text{ kg}\times\text{m}^{-2}$ was 29% lower than that at $22 \text{ kg}\times\text{m}^{-2}$ [IRR: 0.71 (95% CI: 0.53–0.94)], while the IR at $18 \text{ kg}\times\text{m}^{-2}$ was 12% lower [IRR: 0.78 (95% CI: 0.54–1.13)]. BMI at age 30 years was associated with a 2% decreased IR for every 5-unit increment [IRR: 0.98 (95% CI: 0.87–1.12)].

For advanced prostate cancer, BMI at baseline age was associated with a 4% increased IR [IRR: 1.04 (95% CI: 0.88–1.22)], whereas BMI at age 30 years was associated with a 10% decreased IR [IRR: 0.90 (95% CI: 0.73–1.11)], both for every 5-unit increment.

For fatal prostate cancer, BMI at baseline age was associated with a 12% increased MR [MRR: 1.12 (95% CI: 0.87–1.43)], while BMI at age 30 years was associated with a 27% decreased MR [MRR: 0.73 (95% CI: 0.53–1.02)], both for every 5-unit increment.

5.1.2 Updated analyses with extended follow-up

For localized prostate cancer, BMI at baseline age showed an inverse-U association, regardless of whether it was modeled using FP2($-2, -2$) (green line), FP2($-1, 0.5$) (purple line),²¹ or RCS (blue line) (figure 5.2). From the categorical analysis, the multivariable-adjusted IR for the obese men at baseline (BMI ≥ 30 kg \times m⁻²) was 21% lower than that for men in the referent category (21.0–22.9 kg \times m⁻²) [IRR: 0.79 (95% CI: 0.64–0.98)] (table B.3).

For advanced prostate cancer, BMI at baseline age was associated with a 11% increased IR for every 5-unit increment [IRR: 1.11 (95% CI: 0.96–1.27)] (table B.3). No evidence of non-linearity was observed from the RCS model ($p_{\text{non-linearity}} = 0.30$) (figure 5.2).

For fatal prostate cancer, BMI at baseline age was associated with a 12% increased MR for every 5-unit increment [MRR: 1.12 (95% CI: 0.95–1.32)] (table B.3). Again, no evidence of non-linearity was observed ($p_{\text{non-linearity}} = 0.49$) (figure 5.2).

No evidence against the PH assumption was observed for any of the exposure-outcome associations. For example, figure 5.1 shows the time-varying MRR of fatal prostate cancer for BMI at baseline age ≥ 30 kg \times m⁻² versus 21.0–22.9 kg \times m⁻², where the time-dependent coefficient for BMI was modeled using RCS with 3 knots placed at the 10th, 50th, and 90th percentiles of the distribution of the uncensored event times (Discacciati et al., 2015c).²² The p -value relative to the test against the null hypothesis $H_0 : \gamma_1 = \gamma_2 = 0$ was equal to 0.91 [see equation (2.8)].

Lastly, no evidence of heterogeneity by county of residence at baseline was observed, as shown in table 5.1.

Updated results for BMI at 30 years of age are reported in table B.4 and in figure A.3. Overall, the results based on the updated data were consistent with those reported in Paper I, and generally more precise.

Table 5.1: Heterogeneity by county of residence at baseline (Västmanland/Örebro) in the association between BMI at baseline age and localized, advanced, and fatal prostate cancer

Outcome	BMI at baseline age		$P_{\text{heterogeneity}}$
	Västmanland	Örebro	
Localized prostate cancer ^a	0.68 (0.44–0.91)	0.74 (0.49–1.00)	0.35
Advanced prostate cancer ^b	1.13 (0.95–1.35)	1.08 (0.90–1.30)	0.71
Fatal prostate cancer ^c	1.20 (0.96–1.51)	1.05 (0.85–1.30)	0.36

^a Multivariable-adjusted IRR comparing a BMI of 35 kg \times m⁻² with a BMI of 22 kg \times m⁻² from the FP2($-2, -2$) model.

^b Multivariable-adjusted IRR for every 5-unit increment.

^c Multivariable-adjusted MRR for every 5-unit increment.

²¹The best-fitting FP2 in the updated data according to AIC.

²²Corresponding to 65.5, 79.8, and 87.2 years of attained age.

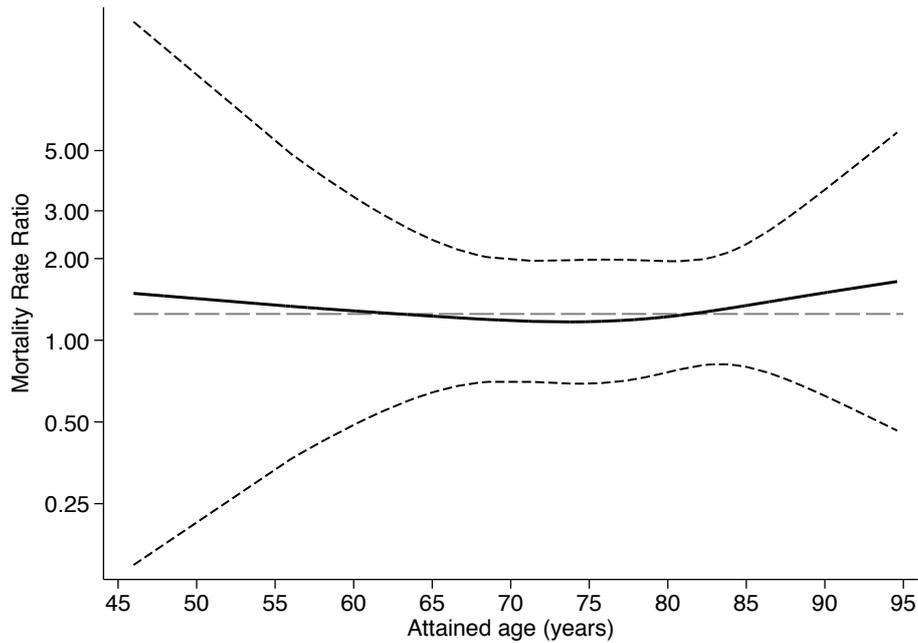


Figure 5.1: Time-varying MRR from prostate cancer for BMI at baseline age $\geq 30 \text{ kg}\times\text{m}^{-2}$ versus $21.0\text{--}22.9 \text{ kg}\times\text{m}^{-2}$ (solid black line). The dashed black lines are 95% confidence interval. The long-dashed grey line is the time-fixed MRR, equal to 1.25 (table B.3). The vertical axis is on the natural log scale.

5.2 Paper II

In Paper II we proposed the use of Laplace regression to estimate percentiles of attained age at the time of the event of interest. We also discussed the consequences in the interpretation of the survival curve in the presence of delayed entries.

5.2.1 Estimating percentiles of attained age at the event

Defining the time scale

An important consideration when analyzing the distribution of survival time is the choice of the time scale. In particular, the difference between the origin of the time scale — that is, that point in time when the subjects become at risk of experiencing the event of interest — and the time at which subjects start to be actually followed-up merits particular attention.

In randomized experimental studies, for example, subjects are typically considered to become at risk at the time of their random allocation to either the treatment or placebo arm. In such cases, the most natural time scale is ‘time since randomization’ (or ‘follow-up time’), which takes value 0 at randomization. Given this sampling design, sometimes called ‘sampling the inflow’, the start of the observation period coincides with the time at which individuals become at risk.

In observational epidemiologic studies, on the other hand, attained age is often a more natural time scale as compared with time since some arbitrary baseline event (Korn et al., 1997; Thiébaud and Bénichou, 2004; Cologne et al., 2012). In this case, the time at which

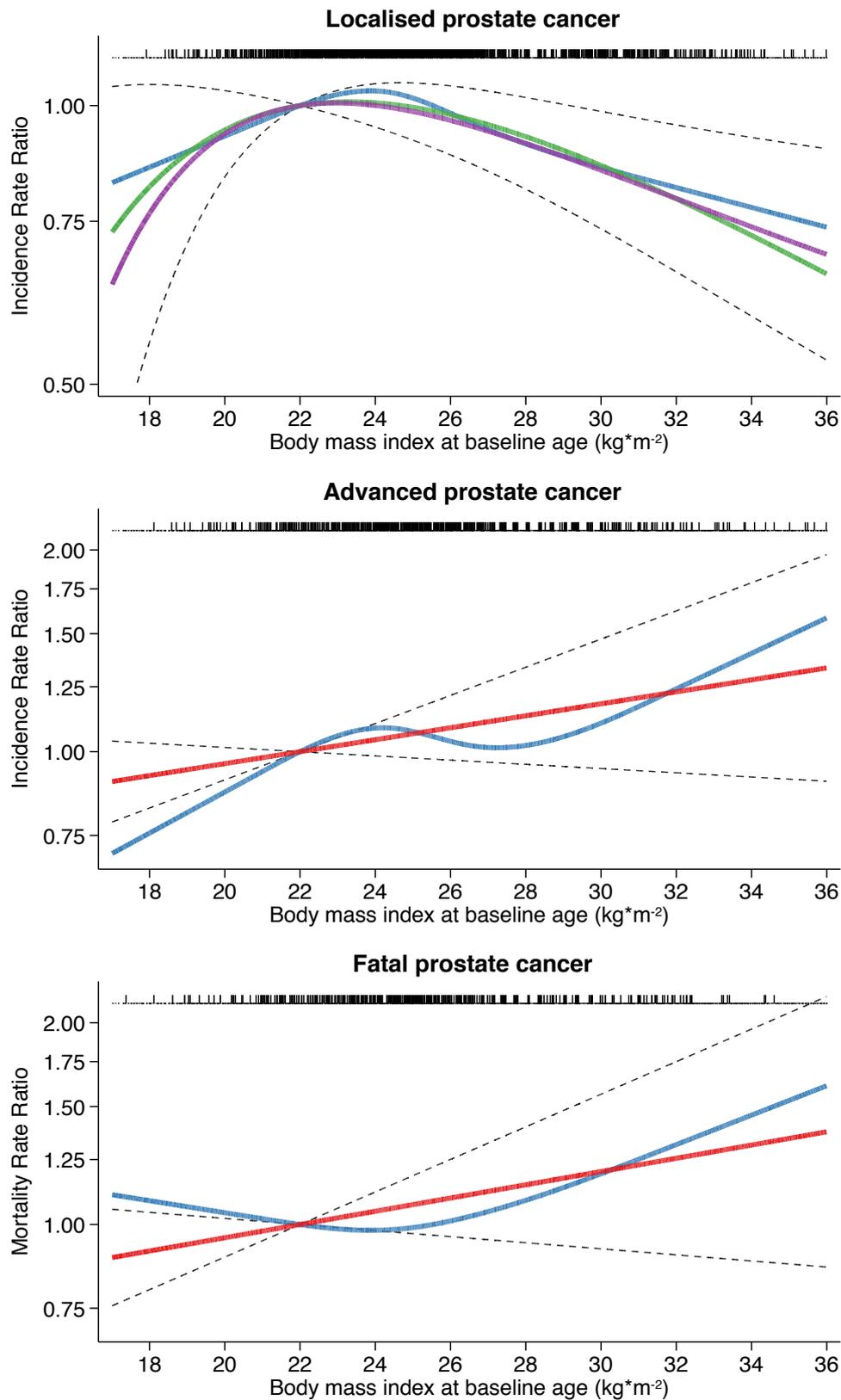


Figure 5.2: Multivariable-adjusted associations of BMI at baseline age ($\text{kg}\times\text{m}^{-2}$) with IR of localized and advanced prostate cancer, and with MR of fatal prostate cancer in the updated analysis of Paper I. BMI was modeled using FP2(-2, -2) (green line), FP2(-1, 0.5) (purple line), RCS with 4 knots (blue line), and in a linear fashion (red line). The referent value was set at $22\text{ kg}\times\text{m}^{-2}$. Vertical lines above the curves represent cases of prostate cancer. The vertical axes are on the natural log scale.

individuals become at risk does not necessarily coincide with the start of the observation period. This situation is referred to as ‘delayed entry’ — that is, individuals become at risk before entering the study. Delayed entries introduce left-truncation, which means that some subjects are excluded from the study because they either died or experienced the event before observation began (Harrell, 2001, section 16.2; Rabe-Hesketh and Skrondal, 2012, part VII). As a result, an extra piece of information, $T_{\text{entry},i}$, has to be added next to $Y_i = \min(T_i, C_i)$ and d_i in order to be able to describe the survival experience of the i -th individual.

In the specific case of COSM and prostate cancer, age is arguably a more meaningful time scale than time since baseline, which corresponds to the time when participants returned the self-administered questionnaire. As a consequence, describing the distribution of age at first diagnosis seems more natural than describing the distribution of time elapsed between baseline and diagnosis.

Figure 5.3 (panel A and B) exhibits the consequences of changing the time scale to the survival experience of 10 random subjects from the COSM. In particular, in panel A the time scale was follow-up time. Here, the beginning of the observation period coincided with the time men were considered to become at risk (baseline, or 1 January 1998, or ‘time 0’). On the other hand, in panel B the time scale for the same 10 individuals was changed to attained age, which introduced delayed entries.

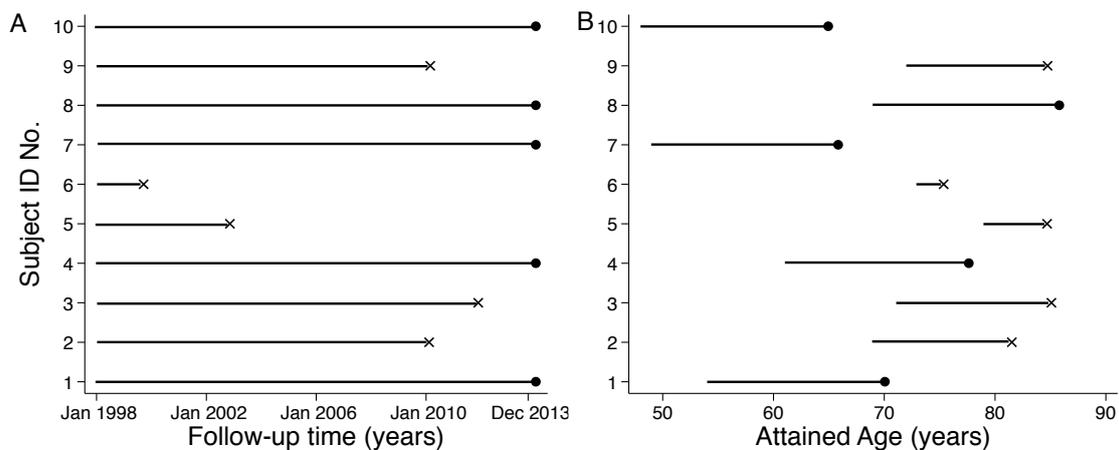


Figure 5.3: Consequences of changing the primary time scale in a prospective cohort study from follow-up time to attained age. Panels A and B illustrate the observation period for a subset of 10 participants followed up until prostate cancer diagnosis (cross) or censoring (dot).

Consequences of delayed entries on the hazard and survival functions

The advantage of working with the hazard function is that it is not affected by delayed entries — that is, by conditioning on survival until a given t_{entry} . This is, of course, because the hazard $h(t)$ is already conditioned on being event-free at time t [equation (2.2)], and therefore it makes no difference to additionally condition on survival until $t_{\text{entry}} < t$. As a consequence, the interpretation of the hazard function does not change.

The survival function on the other hand, given its unconditional nature, is impacted by the change in the time scale. Because of the presence of delayed entries, the survival function is no longer estimating $S(t)$, but rather $S(t)/S(t_{\min}) = S(t|t_{\min})$, where $t_{\min} = \min(t_{\text{entry},1}, \dots, t_{\text{entry},n})$ is the earliest entry time (Lawless, 2003, section 3.5.1; Cleves et al., 2010, section 8.2.3; Mackenzie, 2012). Despite this, the interpretation of the survival curve, and in particular of the survival percentiles, remains difficult. In fact, it is no longer true that the $100p$ -th survival percentile obtained from the survival curve — as illustrated in figure 2.7 — corresponds to the age by which $100p\%$ of the study population has experienced the event of interest.

For example, figure 5.4 shows the survival curves for prostate cancer incidence in the COSM over the period 1998–2012 by county of enrollment, using age as the time scale. The survival curves were obtained from a flexible hazard model using equation (2.9). Due to delayed entries introduced by choosing attained age as the time scale, 65 years of age cannot be interpreted as the age by which 5% of the men recruited in the Västmanland county developed prostate cancer. As an extreme example of why this is so, think that less than 5% of the study participants from Västmanland county might have in theory entered the COSM study by 65 years of attained age.

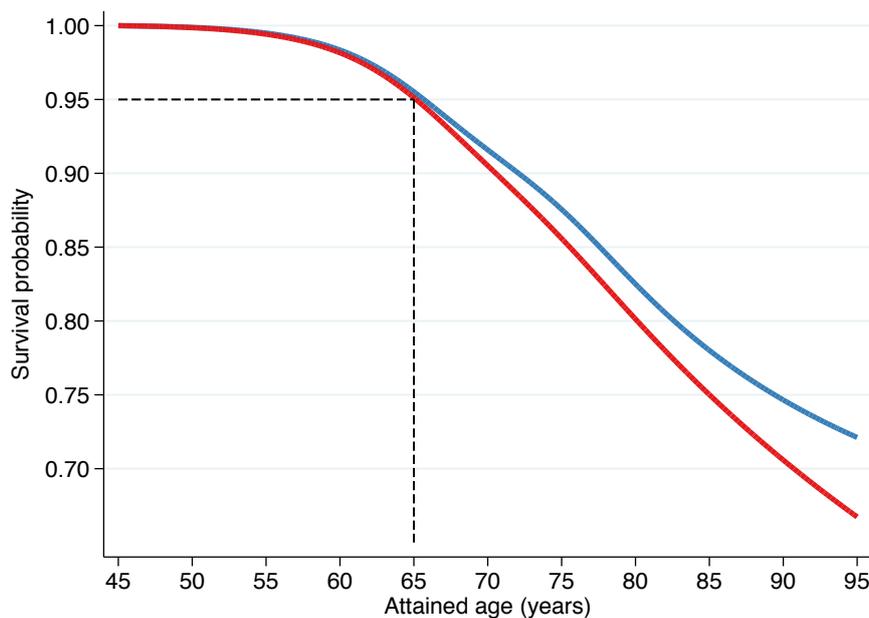


Figure 5.4: Survival curves for prostate cancer incidence in the COSM by county of enrollment, using attained age as the time scale. Survival curves were obtained from a flexible hazard model with a time-dependent coefficient for the enrollment county variable. Baseline hazard was modeled using RCS with 5 knots. The red line refers to Västmanland county, while the blue line refers to Örebro county.

An intuitive way to circumvent this issue, and to obtain survival percentiles that are directly interpretable, is to condition the survival curve on the unique entry times (baseline ages, in our case). By doing so, the $100p$ -th survival percentile of age at the event can be interpreted as the age by which $100p\%$ of the subjects have experienced the event, conditional on a given

baseline age.

Use of quantile regression to model and predict percentiles of attained age at the event

Modeling and predicting survival percentiles of age at the event, conditionally on age at baseline, is straightforward with quantile regression for censored data. This can be done through the following model:

$$Q_{A_i}(p|\text{ageBaseline}_i) = \beta_0(p) + \sum_{r=1}^b \beta_r(p)g_r(\text{ageBaseline}_i), \quad (5.1)$$

where A_i is age at the event and ageBaseline_i is the baseline age for the i -th individual — that is, the individual's entry time.

Age at baseline can be modeled using b flexible transformations, such as RCS or fractional polynomials. Conversely, $b = 1$ and $g_1(\cdot)$ equal to the identity function impose a linear relationship between age at entry and the p -th percentile of age at the event. In this case, for diseases whose occurrence increases with age (such as prostate cancer mortality), one would generally expect to observe a positive regression coefficient $\beta_1(p)$.

Model 5.1 can be easily extended to include other covariates. For example, one could include a binary variable e_i in the model

$$Q_{A_i}(p|\text{ageBaseline}_i, e_i) = \beta_0(p) + \sum_{r=1}^b \beta_r(p)g_r(\text{ageBaseline}_i) + \beta_{b+1}(p)e_i. \quad (5.2)$$

In this case, for a given p , $\beta_{b+1}(p)$ expresses the difference in the $100p$ -th percentile of age at the event between exposed ($e_i = 1$) and unexposed ($e_i = 0$), conditional on age at baseline. For example, if $p = 0.5$, the coefficient $\beta_{b+1}(0.5)$ estimates the differences in median age at the event, conditional on baseline age. An implicit assumption of Model 5.2 is that the association between the covariate e and the $100p$ -th percentile of age at the event is constant across levels of age at baseline. This assumption can be relaxed by including in the model the necessary product terms between $g_r(\text{ageBaseline}_i)$ and e_i .

For example, let e_i take value 1 for those men enrolled in Västmanland county and value 0 for those enrolled in Örebro county. Based on Model 5.2, the predicted 5th and 10th percentiles of age at prostate cancer diagnosis were, for 65-year-old men residing in Örebro county, equal to 71 and 76 years, respectively. The between-county difference in the 5th percentile of age at prostate cancer diagnosis was -6 months, while the 10th PD was -10 months, conditional on baseline age. A richer picture of the association between county of enrollment and percentiles of age at diagnosis is shown in figure 5.5.

More generally, the quantile regression model can be written as

$$Q_{A_i}(p|\text{ageBaseline}_i, \mathbf{x}_i) = \beta_0(p) + \sum_{r=1}^b \beta_r(p)g_r(\text{ageBaseline}_i) + \sum_{j=1}^k \beta_{b+j}(p)x_{ij}. \quad (5.3)$$

The considerations made for model (2.10) apply to model (5.3) as well. In particular, the interpretation of the coefficients is appealing, as they are interpreted as differences in percentiles of attained age at the time of the event.

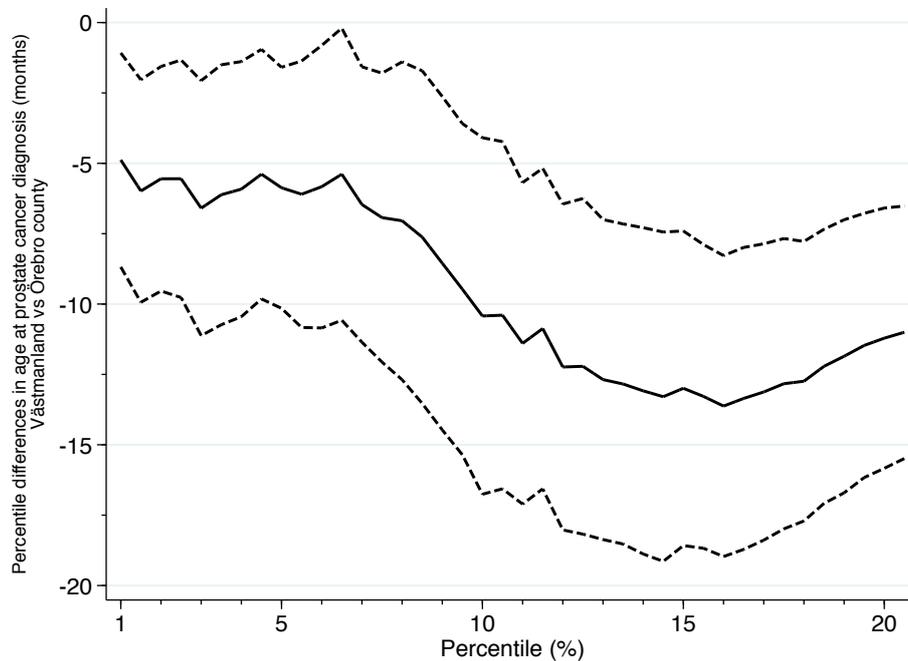


Figure 5.5: First 20 percentile differences (expressed in months) of age at prostate cancer diagnosis between men enrolled in Västmanland county and men enrolled in Örebro county, conditional on baseline age. The solid line is the point estimate, while dashed lines are 95% confidence intervals.

5.2.2 Body mass index and attained age at prostate cancer death

To illustrate the use of quantile regression to model percentiles of attained age at the event, we will briefly re-analyze the updated data presented in section 5.1.2. The aim is to evaluate the association between BMI and age at prostate cancer death.

As reported in section 5.1.2, BMI at baseline was modeled using RCS with 4 knots. Laplace regression was used to model the 5th percentile of age at death adjusting for total energy intake (kcal), total physical activity (MET-h/day), education (years), smoking status (current, former, never smoker), family history of prostate cancer (yes, no, don't know), personal history of diabetes (yes, no), county of enrollment (Västmanland, Örebro), BMI at age 30 years ($\text{kg}\times\text{m}^{-2}$), and age at baseline (years).

For every 5-unit increment in BMI the 5th percentile of age at prostate cancer death decreased by 4 months, although the 95% CI was observed to be quite wide (-13 to 5 months). No evidence of a non-linear association was observed ($p_{\text{non-linearity}} = 0.41$). Although the magnitude of the 5th percentile difference (4 months) is not comparable with the magnitude of the MRR estimated from the Cox PH model, the directions of the associations are consistent. In particular, the negative coefficient from Laplace regression and the positive coefficient from Cox regression model (log-mortality rate ratio) indicate a worse survival, when it comes

to prostate cancer mortality, among overweight and obese men as compared with lean and normal-weight men.

Figure 5.6 shows the dose–response association between BMI at baseline and differences in the 5th percentile of age at prostate cancer death.

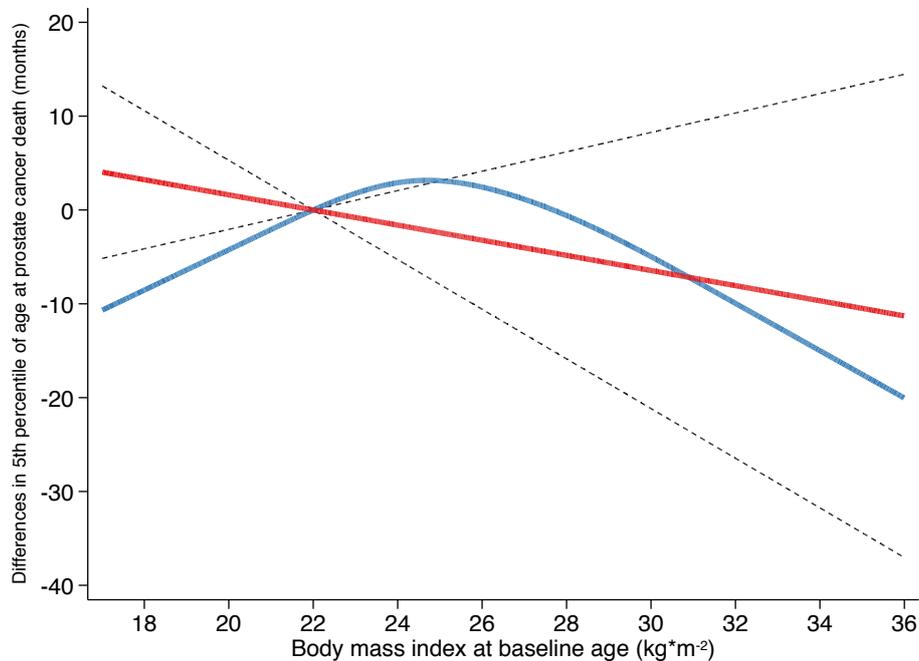


Figure 5.6: Multivariable-adjusted differences in the 5th percentile of age at prostate cancer death by levels of BMI at baseline. BMI was modeled using RCS with 4 knots (blue line), and in a linear fashion (red line). The referent value was set at 22 kg·m⁻². Black dashed lines represent the 95% confidence interval for the linear model.

Results for the first 4 PDs in age at prostate cancer death were, for every 5-unit increment in BMI, −2 (95% CI: −14 to 9), −3 (95% CI: −12 to 6), −3 (95% CI: −13 to 6), and −4 (95% CI: −14 to 6) months.

5.3 Paper III

In this paper we reviewed the definition of RAP and its estimation, and critically discussed certain misinterpretations appeared in the epidemiologic literature. Furthermore, we showed how RAP estimation is sensitive to the specification of the age-disease association.

5.3.1 Misinterpretations of risk and rate advancement periods

We identified three major misinterpretations of RAP: first, equating RAP with the difference in mean survival times; second, interpreting RAP as the time by which the survival curve for the exposed individuals is shifted compared with that for the unexposed; third, equating the RAP to a simple ratio of two logRRs.

RAP as a difference in mean survival time

The most common misinterpretation of RAP equates it with difference in mean survival time. The two are, however, profoundly different quantities and using the former to estimate the latter will inevitably lead to flawed conclusions.

Definition of RAP is given in equation (2.17) and is interpreted as the difference in baseline age at which exposed individuals (e_1) reach the same rate of the disease as unexposed individuals (e_0), under the assumption of a monotonic increase in event rate over age and conditional on disease-free survival to some baseline age.

Mean survival time, on the other hand, equals the area under the survival curve (Muldowney et al., 2012). Consequently, difference in mean survival time between unexposed and exposed individuals is defined as:

$$\mu_{e_0} - \mu_{e_1} = \int_0^{+\infty} S(t|e_0)dt - \int_0^{+\infty} S(t|e_1)dt,$$

and is interpreted as the difference in the mean (expected) survival time between unexposed and exposed subjects.

Table 5.2 reports synthetic data from an hypothetical cohort study with 10 exposed and 10 unexposed participants, including age at baseline in years, followed up for 36 months. Fitting a Cox PH model to these data, with baseline age and exposure as covariates, resulted in an estimated $\widehat{\text{RAP}} = 1.594/0.109 = 14.6$ years, as per equation (2.20). Thus, under the model, we would expect exposed subjects to experience the same disease rate as that among unexposed subjects who were 14.6 years older at baseline.

To calculate difference in survival time for the same data, we estimated the two survival curves from the PH model previously fitted, one for exposed and one for unexposed subjects, fixing baseline age to the sample mean (57 years) [equation (2.6)]. The estimated difference in mean survival between exposed and unexposed was equal to 9.2 months. Therefore, under the model, we would expect the exposed subjects to live 9.2 months less as compared with the unexposed subjects. This means that if one were to employ RAP to estimate mean–survival difference, one would overestimate the latter by more than 13 years or, equivalently, over 19-fold.

There are other distinctions between RAP and difference in mean survival time that are worth to be mentioned. First, the estimated RAP can be larger than the maximum follow-up

Table 5.2: Data from an hypothetical cohort study of 20 individuals (10 exposed and 10 unexposed) followed up for 36 months

Unexposed	Follow-up (months) ^a	6	6+	7	11+	16	16	19+	22	23	36
	Baseline age (years)	67	65	58	61	67	62	50	58	47	52
Exposed	Follow-up (months) ^a	1	4+	5	6	6+	6	11	12+	15	22
	Baseline age (years)	61	67	58	49	52	56	50	49	51	57

^a + indicates a censored observation.

time, while the difference in mean survival must by definition be smaller than the largest follow-up time. Second, mean survival can be estimated only if one observes the upper tail of the survival distribution, which is often not the case due to censoring. This is true unless one is willing to assume some parametric distribution for the p.d.f. of survival time T and then extrapolate the survival curve beyond the observed follow-up period. Third, the unit of measurement of RAP is only determined by that of baseline age, and has nothing to do with the unit of measurement of follow-up time. This means that if in table 5.2 the follow-up times were days instead of months, RAP would still be 14.6 years, but the difference in mean survival time would become 9.2 days.

RAP as a shift of the survival curve

RAP has been interpreted as “by how many months or years the survival curve among the exposed is ‘advanced’ or brought forward compared with the survival curve among the unexposed” (Brunekreef et al., 2007). However, under PH, RAP is the difference in baseline age for which the survival curve for the unexposed individuals is equal to the survival curve for the exposed individuals, given that all other covariates are kept constant. In other words, RAP is the difference in baseline ages $a_0 - a_1$ such that $S(t|e_0, a_0, \mathbf{c}) = S(t|e_1, a_1, \mathbf{c})$.

In fact, under PH, equation (2.6) holds and by taking the complementary log-log transformation of $S(t|e, a, \mathbf{c})$, one obtains

$$\log [-\log [S(t|e, a, \mathbf{c})]] = \log [-\log [S_0(t)]] + \beta_1 e + \beta_2 g(a) + \sum_{i=1}^k \beta_{i+2} c_i,$$

from which equation (2.19) immediately follows.

RAP can therefore be equally defined as the difference in baseline age by which a group of e_1 -exposed subjects experiences the same survival as e_0 -exposed subjects, assuming a strictly increasing disease rate over age and disease-free survival to baseline age.

RAP as a concept similar to relative risk

R Rs measure the association between an exposure and the occurrence of a disease. Although they may vary with age, they do not conceptually depend on age. RAP, on the other hand, are not measures of association in the traditional sense, but rather they measure the exposure dependence of a relation between age and disease. As Brenner et al. (1993) pointed out “given a fixed magnitude of the exposure-disease association, risk or rate advancement periods are inversely related to the age gradient of disease risk or rate”. In particular, even strong exposure-disease associations can be dominated by the age effect, depending on the strength of the age disease association, resulting in short advancement periods.

To illustrate this point, imagine two diseases, d_1 and d_2 , whose rates $h_1(a, e)$ and $h_2(a, e)$ are functions of a binary exposure e and age at baseline a (measured in years). In particular, $h_1(a, e) = k_1 4^e a^5$ and $h_2(a, e) = k_2 1.1^e a^{1/5}$, where k_1 and k_2 are baseline rates, possibly depending on follow-up time. The exposure-disease association is stronger for d_1 (RR = 4)

than for d_2 (RR = 1.1), at any given baseline age. After logarithmic transformation of these models, the RAP for d_1 is found from

$$\log(k_1) + 5 \log(a_0) = \log(k_1) + \log(4) + 5 \log(a_1),$$

which gives $(4^{1/5} - 1)a_1 = 0.32a_1$; similarly, RAP for d_2 is $(1.1^{1/5} - 1)a_1 = 0.61a_1$ [see equation (2.21)]. Therefore, RAP is greater for d_2 than for d_1 at any baseline age, despite the RR being higher for d_1 than for d_2 .

This simple example shows the fact that strong associations — that is, large RRs — need not lead to a large RAP, or vice versa. RAP thus provide a different perspective on RRs and shows that even exposures that are strongly positively associated with the occurrence of the disease may not turn out to be important from a public-health point of view, if what they do is to shift a very steep age-incidence curve by a short time period.

5.3.2 Misspecification of the age-disease association

Estimation of RAP is particularly sensitive to the form of the age-disease dependence $g(a)$ in the rate or risk model. This means that if the true association between the occurrence of the disease and baseline age is non-linear, including age in the model as a linear term ($g(a) = a$) can severely bias the RAP estimates.

Suppose for example that the risk r of a disease d follows the logistic model

$$\text{logit}(r) = -10 + \log(2)e + 2\log(a). \quad (5.4)$$

From equation (2.21), RAP at baseline age a_1 is equal to $0.414a_1$, so that, between baseline ages of, say, 45 and 80 years, RAP increases from 11.7 to 20.8 years.

To assess the bias deriving from misspecifying the functional form of age, we carried out a simulation from a population in which exposure e followed a Bernoulli(0.5) distribution, baseline age a followed a Uniform(45,80) distribution (independent of e), and d was randomly generated from the logistic model (5.4). Taking 2,000 samples of size 500 each, we estimated RAP from the misspecified logistic model $\text{logit}(r) = \beta_0 + \beta_1e + \beta_2a$. The mean and median simulated RAP estimates were 25.4 and 21.5 years, constant over baseline age, not even in the correct range — that is, between 11.7 and 20.8 years. Figure 5.7 shows the distribution of the 2,000 RAP estimates from the misspecified model.

5.3.3 Body mass index and prostate cancer mortality rate advancement period

Using the updated COSM data presented in section 5.1.2, we observed no evidence of non-linearity between baseline age and prostate cancer MR ($p_{\text{non-linearity}} = 0.18$) and, at the same time, the assumption of monotonicity in the age-disease association seemed to hold (data not shown).

Based on equation (2.20), the RAP comparing obese men at baseline ($\geq 30 \text{ kg}\times\text{m}^{-2}$) with normal-weight men ($21.0\text{--}22.9 \text{ kg}\times\text{m}^{-2}$) was equal to 18 months. Therefore, under the

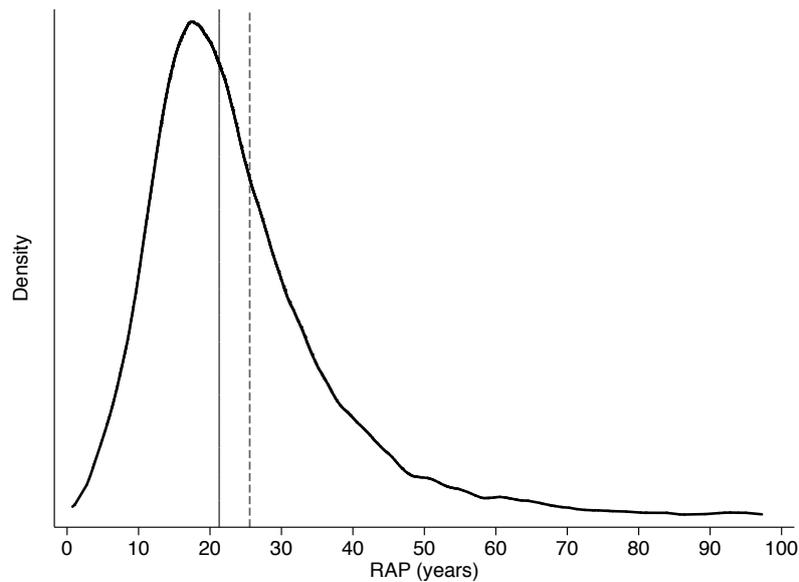


Figure 5.7: Distribution of 2,000 RAP estimates from the misspecified logistic model in the simulation study. The dashed vertical line indicates the mean of the distribution (25.4 years), while the solid vertical line indicates the median (21.5 years).

model, one would expect obese men to experience the same prostate cancer MR as that among normal-weight men who were 18 months older at baseline. The RAP for every 5-unit increment in BMI was equal to 8 months.

Even if there was not enough evidence to reject the linearity assumption in the age-disease relation, the sensitivity of the previous estimates was examined by modeling age with a natural logarithm transform [equation (2.21) for RAP applies]. The RAP comparing obese men ($\geq 30 \text{ kg}\times\text{m}^{-2}$) with normal-weight men ($21.0\text{--}22.9 \text{ kg}\times\text{m}^{-2}$) was equal to 11 months for men aged 45 years old at baseline and 17 months for men aged 70 years old. The RAP for every 5-unit increment in BMI increased linearly from 5 to 7 months for men aged 45 and 70 years old, respectively. This, again, illustrates the high sensitivity of RAP to the form of the age-disease dependence.

5.4 Paper IV

Aim of this paper was to summarize the existing epidemiologic evidence — available as aggregated data — on the dose–response association between BMI and the incidence of localized and aggressive prostate cancer. Furthermore, possible differences in the dose–response association according to study-level covariates were investigated. Only prospective studies were included in this meta-analysis.

5.4.1 Main results

Random-effect dose–response meta-analysis

For localized prostate cancer, we observed a 6% decreased incidence for every 5-unit increment in BMI [RR: 0.94 (95% CI: 0.91–0.97)]. No evidence of a non-linear relationship was found when BMI was modeled using a quadratic polynomial ($p_{\text{non-linearity}} = 0.10$). In the linear model, there was no evidence of heterogeneity ($p_{\text{heterogeneity}} = 0.27$, $I^2 = 18\%$) or publication bias ($p_{\text{publication bias}} = 0.35$ from the Egger’s test).

For advanced prostate cancer, we found a 9% increased incidence for every 5-unit increment in BMI [RR: 1.09 (95% CI: 1.02–1.16)]. Again, no evidence of non-linearity was observed ($p_{\text{non-linearity}} = 0.10$). There was, however, a moderate amount of between-study heterogeneity ($p_{\text{heterogeneity}} = 0.08$, $I^2 = 38\%$) and evidence of publication bias ($p_{\text{publication bias}} = 0.02$). A large part of the observed heterogeneity was due to one single study conducted in Australia, that reported a RR of 1.51 (95% CI: 1.14–2.01) (MacInnis et al., 2003). Removing this study led to a decrease in the between-study variability ($p_{\text{heterogeneity}} = 0.26$, $I^2 = 18\%$), while the pooled RR for every 5-unit increment in BMI changed only marginally [RR: 1.07 (95% CI: 1.01–1.13)].

Meta-regression and sensitivity analysis

By means of meta-regression, we assessed whether the dose–response associations differed according to the following study-level characteristics: method of BMI collection (trained personnel versus self-reported measurements), and degree of adjustment (adjustment for physical activity and personal history of diabetes versus adjustment for only one or neither of these covariates). However, we did not observe evidence of effect modification by these study-level covariates, neither for localized nor for advanced prostate cancer.

Since the dose–response meta-analysis could have been sensitive to the choice of the BMI level assigned to the open-ended categories (Crippa et al., 2015), we carried out a sensitivity analysis assuming that the amplitude of the open-ended categories was twice that of the neighborhood categories. In this scenario, the RRs for every 5-unit increment in BMI were observed to be 0.95 (95% CI: 0.93–0.98) and 1.07 (95% CI: 1.01–1.13) for localized and advanced prostate cancer, respectively.

Lastly, we performed a series of sensitivity analyses regarding the classification criteria used in some of the studies. First, in the meta-analysis on localized prostate cancer, we pooled the results for ‘moderate grade’ (Gleason score 5–7) with those for ‘low grade’ prostate cancer (Gleason score 2–4) in the study by MacInnis et al. (2003). Second, in the meta-analysis on advanced prostate cancer, we pooled the results for ‘non-metastatic high grade’ with those for ‘stage D or fatal’ cases in the study by Rodriguez et al. (2007). Third, we used the classification criterion based on Gleason score instead of the that based on the TNM staging system in the study by Pischon et al. (2008). Fourth, we excluded from the meta-analysis on localized prostate cancer those three studies that used Gleason score as the only criterion to classify

incident cases (Cerhan et al., 1997; MacInnis et al., 2003; Putnam et al., 2000). The pooled RRs did not appreciably change in any of these sensitivity analyses.

5.4.2 Updated dose–response meta-analysis

Localized prostate cancer

Figure 5.8 shows the 14 study-specific dose–response associations, where BMI was modeled using RCS with 3 knots positioned at the 10th, 50th, and 90th percentiles of the BMI distribution²³ (blue line) and in a linear fashion (red line). The regression model for the i -th study was

$$E(y_{ij}) = \beta_{i1} [g_1(x_{ij}; \boldsymbol{\lambda}) - g_1(x_{i0}; \boldsymbol{\lambda})] + \beta_{i2} [g_2(x_{ij}; \boldsymbol{\lambda}) - g_2(x_{i0}; \boldsymbol{\lambda})],$$

for $i = 1, \dots, 14$ and $j = 1, \dots, J_i$. The functions $g_1(\cdot)$ and $g_2(\cdot)$ were the 2 RCS transformations characterized by the vector $\boldsymbol{\lambda}$ containing the knots position.

The 14 vectors of study-specific regression coefficients $\boldsymbol{\beta}_i$ were then pooled using the random-effect bivariate meta-analysis model

$$\begin{pmatrix} \beta_{i1} \\ \beta_{i2} \end{pmatrix} \sim N_2 \left(\begin{pmatrix} \theta_1 \\ \theta_2 \end{pmatrix}, \begin{bmatrix} \hat{V}(\beta_{i11}) & \hat{V}(\beta_{i12}) \\ \hat{V}(\beta_{i21}) & \hat{V}(\beta_{i22}) \end{bmatrix} + \begin{bmatrix} \psi_{11} & \psi_{12} \\ \psi_{21} & \psi_{22} \end{bmatrix} \right),$$

whose parameters were estimated by REML.

Overall, BMI was associated with the incidence of localized prostate cancer in the RCS model ($p_{\text{overall}} < 0.001$) and evidence of non-linearity was observed ($p_{\text{non-linearity}} < 0.001$), as illustrated in figure 5.9 (blue line). Compared with a BMI of $22 \text{ kg} \times \text{m}^{-2}$, the pooled RRs were 1.01 (95% CI: 0.99–1.04) for $25 \text{ kg} \times \text{m}^{-2}$, 0.93 (95% CI: 0.90–0.98) for $30 \text{ kg} \times \text{m}^{-2}$, and 0.81 (95% CI: 0.74–0.88) for $35 \text{ kg} \times \text{m}^{-2}$. Between-study heterogeneity was marginal ($p_{\text{heterogeneity}} = 0.28$, $I^2 = 12\%$), as measured by the multivariable extensions of the Q test and of the I^2 statistic [equations (2.28) and (2.29)]. BMI was also modeled using RCS with knots placed at the 25th, 50th, and 75th percentiles of the BMI distribution²⁴ (purple line) and a quadratic polynomial (green line), as in Paper IV. These 2 alternative exposure transformations gave very similar results as compared with the main analysis, both in terms of predicted population-average dose–response associations and between-study heterogeneity. Lastly, excluding the study by Gong et al. (2006), which did not report enough data to approximate the covariance between the logRR estimates, did not virtually change the pooled dose–response association, while the between-study heterogeneity decreased to $I^2 = 3\%$ ($p_{\text{heterogeneity}} = 0.42$).

Advanced prostate cancer

Similarly to what described before, figure A.4 exhibits the 18 study-specific dose–response associations between BMI and incidence of advanced prostate cancer. BMI was modeled using

²³Corresponding to 22.0, 26.1, and 32.5 $\text{kg} \times \text{m}^{-2}$.

²⁴Corresponding to 22.8, 26.1, and 28.8 $\text{kg} \times \text{m}^{-2}$.

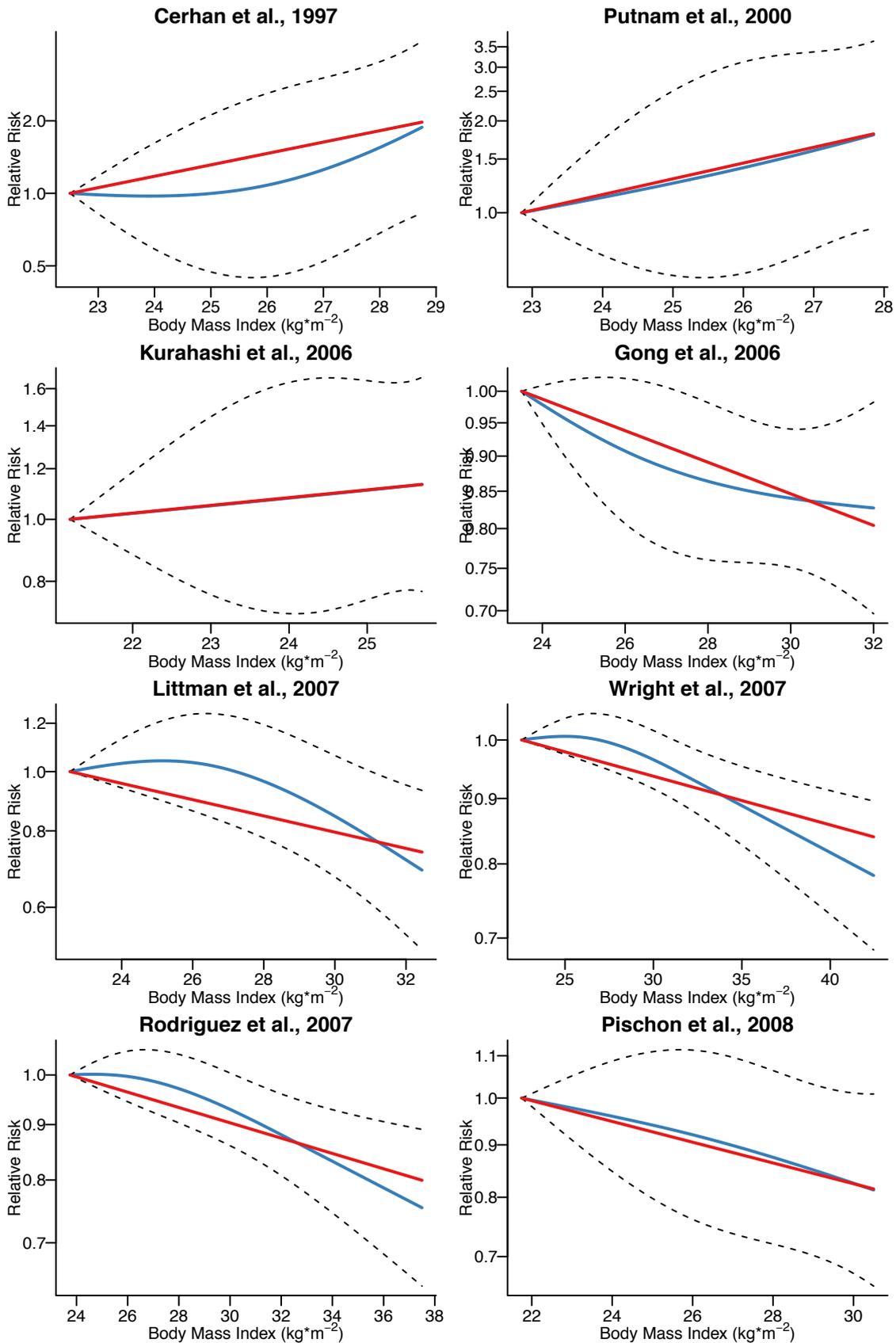
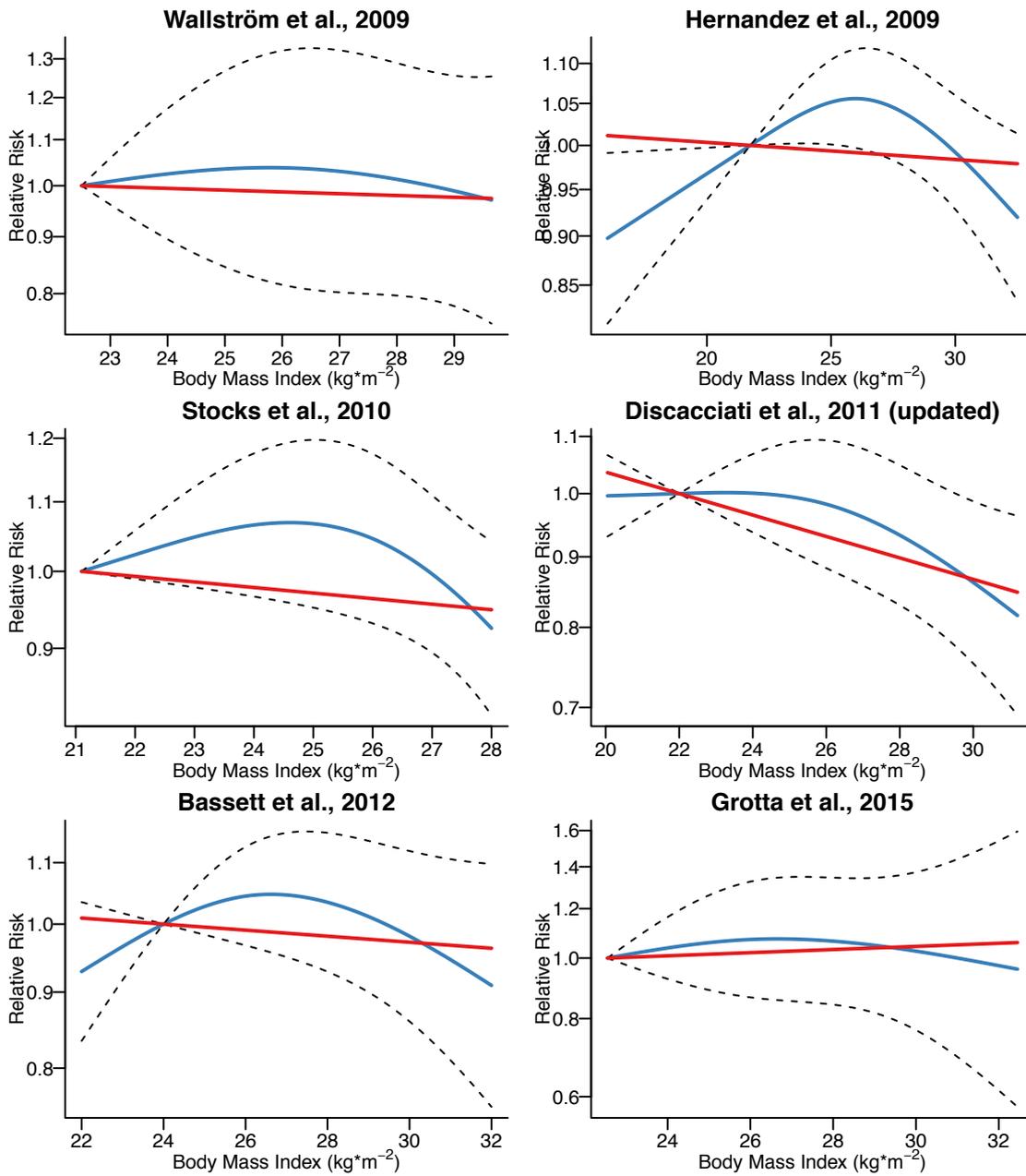


Figure 5.8: Study-specific dose-response associations between BMI and incidence of localized prostate cancer in the updated meta-analysis including 14 prospective studies. BMI was modeled using RCS with 3 knots positioned at the 10th, 50th, and 90th percentiles of the overall BMI distribution (blue line) and in a linear fashion (red line). Dashed black lines represent the 95% CI for the RCS models. The vertical axes are on the natural log scale. Figure continued on next page.



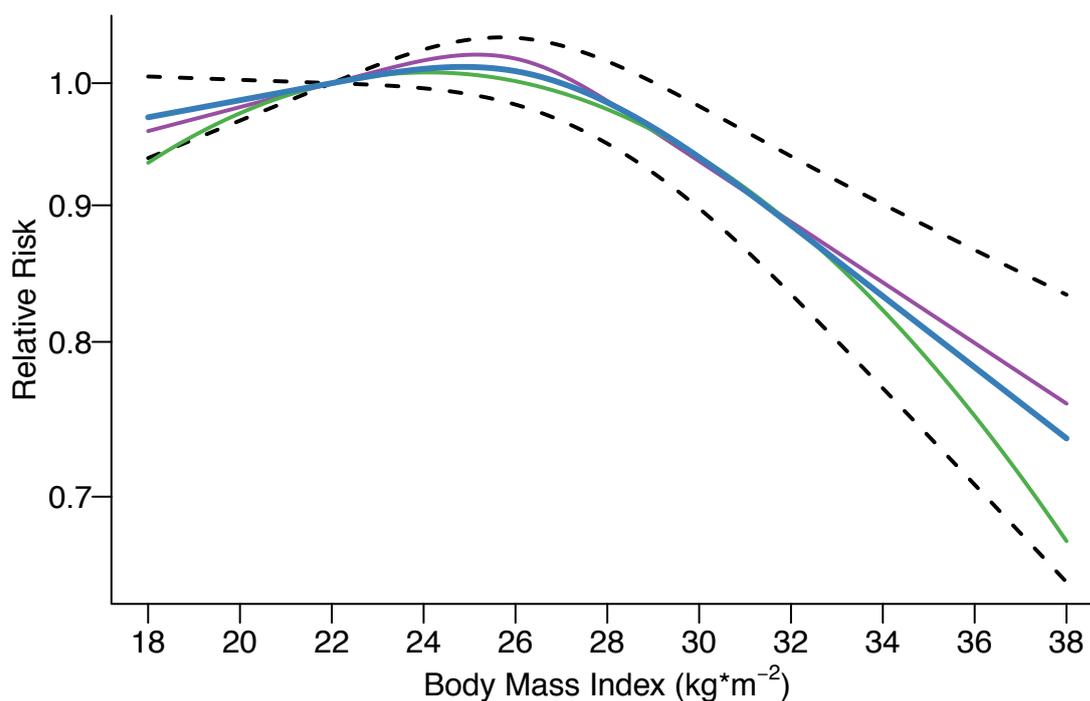


Figure 5.9: Pooled dose–response association between BMI and incidence of localized prostate cancer from a random-effect multivariate meta-analysis. BMI was modeled using RCS with 3 knots positioned at the 10th, 50th, and 90th percentiles of the BMI distribution (blue line), with RCS with 3 knots positioned at the 25th, 50th, and 75th percentiles of the BMI distribution (purple line), and with a quadratic polynomial transformation (green line). Dashed black lines represent the 95% CI for the first RCS model. BMI equal to $22 \text{ kg}\times\text{m}^{-2}$ served as the referent group. The vertical axis is on the natural log scale.

RCS with 3 knots positioned at the 10th, 50th, and 90th percentiles of the BMI distribution²⁵ (blue line) and in a linear fashion (red line). The 18 vectors of study-specific regression coefficients used as the outcome in a random-effect bivariate meta-analysis model.

Although BMI was associated with the incidence of advanced prostate cancer in the multivariate model pooling the study-specific RCS regression coefficients ($p_{\text{overall}} = 0.004$), no evidence of non-linearity was observed ($p_{\text{non-linearity}} < 0.89$) (figure 5.10, blue line). For this reason, study-specific regression coefficients where BMI was modeled in a linear fashion were pooled by means of a univariate random-effect meta-analysis. For every 5-unit increment in BMI, the incidence of advanced prostate cancer was observed to increase by 7% [RR: 1.07 (95% CI: 1.03–1.12)] (red line). Between-study variability was limited as compared to total variability ($p_{\text{heterogeneity}} = 0.15$, $I^2 = 26\%$). Removing those two studies that did not report information about number of cases and person-years by categories of BMI did not appreciably change the results [RR: 1.08 (95% CI: 1.03–1.13) for every 5-unit increment, $I^2 = 27\%$] (Habel et al., 2000; Gong et al., 2006). A forest plot reporting the 18 study-specific RRs for every 5-unit increment in BMI is shown in figure A.5.

²⁵Corresponding to 22.0, 26.0, and 31.6 $\text{kg}\times\text{m}^{-2}$.

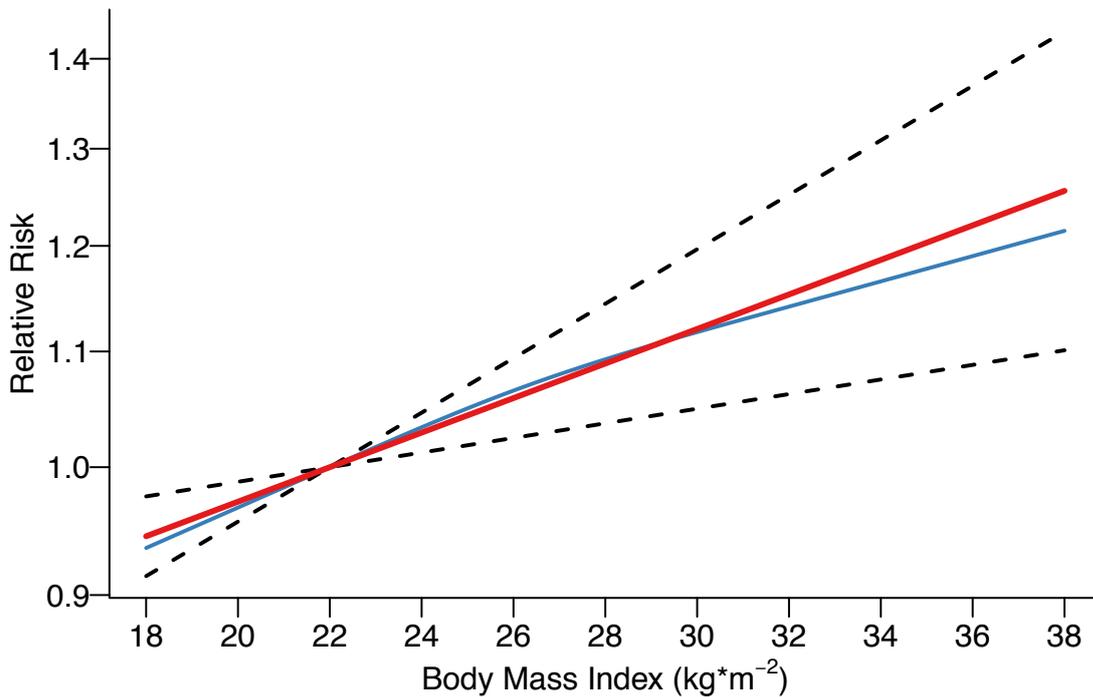


Figure 5.10: Pooled dose–response association between BMI and incidence of advanced prostate cancer from a random-effect multivariate meta-analysis. BMI was modeled using RCS with 3 knots positioned at the 10th, 50th, and 90th percentiles of the BMI distribution (blue line), and in a linear fashion (red line). Dashed black lines represent the 95% CI for the linear model. BMI equal to $22 \text{ kg} \times \text{m}^{-2}$ served as the referent group. The vertical axis is on the natural log scale.

5.5 Paper V

The aim of Paper V was to present, discuss, and practically illustrate 3 tools that can help to evaluate the goodness of fit of a dose–response meta-analysis: deviance, coefficient of determination (R^2), and decorrelated-residuals–versus–exposure plot.

These tools were presented in Paper V using the notation following the ‘one-stage’ or ‘pool-first’ dose–response meta-analytic approach. However, they can be equivalently expressed in terms of notation based on the two-stage approach. In the next sections, we will follow this alternative way of presenting the 3 tools. Note that in the following exposition it is assumed that $\Sigma_i = \mathbf{V}(\boldsymbol{\beta}_i)$ and that the assigned dose x_{i0} for the referent level of the exposure is equal to 0 for all the studies.

5.5.1 Goodness of fit tools for dose–response meta-analysis

Deviance

In dose–response meta-analysis, the data points to be fitted are the non-referent logRRs reported by the single studies. Therefore, analysis of residuals can be useful to evaluate how close reported and predicted logRRs are at each exposure level. Study-specific vectors of resid-

uals, calculated as the difference between the observed logRRs and the model predictions from the overall dose–response function, are equal to

$$\mathbf{e}_i = \mathbf{y}_i - \mathbf{X}_i \mathbf{Z}_i \hat{\boldsymbol{\theta}}.$$

A statistic for the absolute goodness of fit based on these residuals is the deviance statistic, which is defined as

$$D = \sum_{i=1}^K D_i = \sum_{i=1}^K (\mathbf{y}_i - \mathbf{X}_i \mathbf{Z}_i \hat{\boldsymbol{\theta}})^\top \mathbf{S}_i^{-1} (\mathbf{y}_i - \mathbf{X}_i \mathbf{Z}_i \hat{\boldsymbol{\theta}}) = \sum_{i=1}^K \mathbf{e}_i^\top \mathbf{S}_i^{-1} \mathbf{e}_i. \quad (5.5)$$

The deviance measures the total absolute distance between reported and fitted logRRs while taking into account the correlation structure of the study-specific logRRs through the matrices \mathbf{S}_i — that is, the generalized residual sum of squares (GRSS). Intuitively, the smaller the deviation, the closer the reported and predicted logRRs will be.

Building on the assumption that the single logRRs are normally distributed, the deviance provides a test for model specification. Under the null hypothesis that the model is correctly specified, D is asymptotically distributed as a chi-square random variable with $n - qm$ degrees of freedom (df), where $n = \sum_{i=1}^K J_i$. This means that testing for model specification amounts to testing whether, under the null hypothesis, the residual variance corrected for the correlation between the logRRs is larger than one would expect. A small p -value indicates that there is evidence that the posited model fails in accounting for the observed variation among the logRRs.

Coefficient of determination

A descriptive statistic that can be used as a complement to the deviance to summarize the goodness of fit of a given model is the coefficient of determination (R^2). This statistic evaluates the agreement between observed and predicted logRRs and, unlike the deviance, is bounded between 0 and 1 (Hagquist and Stenbeck, 1998; Kvålseth, 1985).

Given that the generalized total sum of squares (GTSS) is equal to $\sum_{i=1}^K \mathbf{y}_i^\top \mathbf{S}_i^{-1} \mathbf{y}_i$, and given the lack of the intercept term, R^2 is defined, following the work of Theil (1961, section 6.2) and Buse (1973), as:

$$R^2 = 1 - \frac{\text{GRSS}}{\text{GTSS}} = 1 - \frac{\sum_{i=1}^K (\mathbf{y}_i - \mathbf{X}_i \mathbf{Z}_i \hat{\boldsymbol{\theta}})^\top \mathbf{S}_i^{-1} (\mathbf{y}_i - \mathbf{X}_i \mathbf{Z}_i \hat{\boldsymbol{\theta}})}{\sum_{i=1}^K \mathbf{y}_i^\top \mathbf{S}_i^{-1} \mathbf{y}_i}.$$

R^2 is a dimensionless index that measures the proportion of the GTSS accounted for by the exposure and study-level covariates. It takes value 0 if the dose–response meta-analytic model explains no variability in the observed logRRs, while it takes value 1 if the model accounts for all the observed variability among the logRRs. Generally, a low R^2 might be an indication that

a more flexible transformation of the exposure and/or a meta-regression model is needed.

An adjusted version of R^2 that is penalized by the number of total covariates included in the first and second stage of the dose–response meta-analysis is given by

$$R_{\text{adj}}^2 = 1 - \frac{n}{n - qm} (1 - R^2).$$

R_{adj}^2 increases only if the increment in R^2 is larger than what would be expected by chance alone and can prove useful to compare the fit of non-nested models.

Visual assessment

Visual inspection of the model fit can reveal important data features and model shortcomings that may otherwise go undetected (Kvålseth, 1985). Visual assessment of the goodness of fit in dose–response meta-analysis is however made more difficult due to the fact that the study-specific logRRs are correlated. As a consequence, the fitted dose–response curve might not even pass through the data points, depending on the particular correlation structure of the residuals, and a simple plot overlaying the dose–response curve to the reported logRRs might therefore be highly misleading. This issue is illustrated in figure 5.11 using the aggregated data reported in table 2.4. This is the reason why, for example, in figure 5.8 we decided to not overlay the observed RRs to the study-specific regression curves. To avoid this problem, one can plot the decorrelated residuals versus the exposure.

The decorrelated residuals are obtained by decomposing each study-specific matrix \mathbf{S}_i through Cholesky factorization, so that $\mathbf{S}_i = \mathbf{C}_i \mathbf{C}_i^\top$, where \mathbf{C}_i is a lower triangular matrix.²⁶ The study-specific decorrelated residuals \mathbf{e}_i^* are then obtained by multiplying the inverse of \mathbf{C}_i by the difference between reported and fitted logRRs:

$$\mathbf{e}_i^* = \mathbf{C}_i^{-1} (\mathbf{y}_i - \mathbf{X}_i \mathbf{Z}_i \hat{\boldsymbol{\theta}}) = \mathbf{C}_i^{-1} \mathbf{e}_i.$$

Lastly, the decorrelated residuals for all the studies are plotted against the exposure.

Although the vertical distances from the reference line drawn at $e^* = 0$ have no meaningful interpretation, it is still possible to assess how the pooled dose–response curve fits the data according to exposure levels. If the fit is perfect, all the points will lie on the reference line. As the fit gets worse, the points will move away from it. A pattern in the decorrelated residuals might indicate for example that the fit of the model is adequate only at certain exposure levels or that study-level covariates need to be taken into account, therefore suggesting the need of a richer dose–response model. Overlaying a LOWESS smoother to the plot or changing the shape/color of the points according to study-level covariates might help to detect such patterns.

²⁶Equivalently, $\mathbf{S}_i^{-1} = (\mathbf{C}_i^{-1})^\top (\mathbf{C}_i^{-1})$.

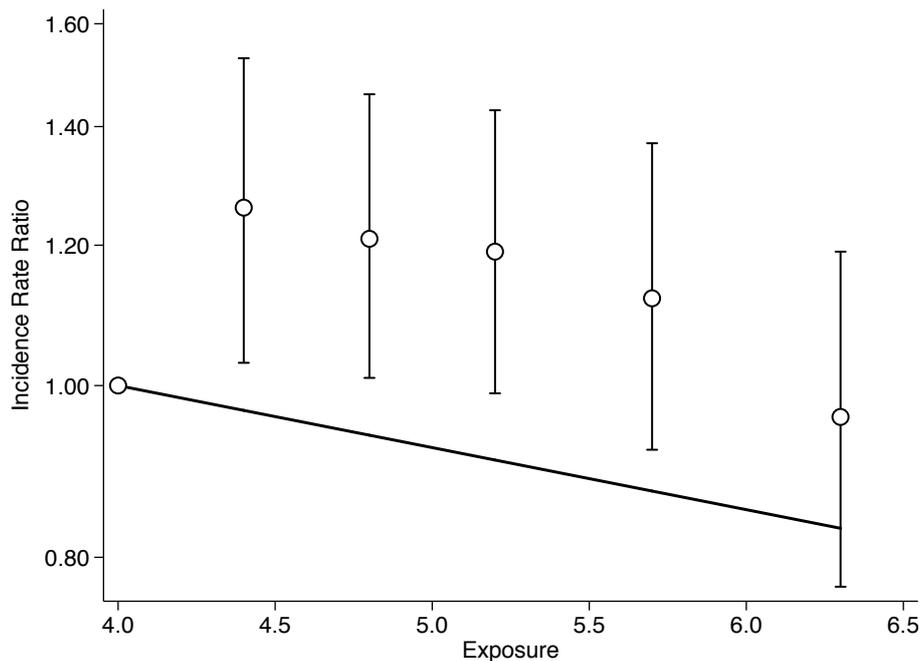


Figure 5.11: Fitted linear trend (solid line) based on IRRs (hollow circles) and exposure values reported in a single study (table 2.4). Due to the correlation among the IRRs, the linear trend does not pass through the data points. The vertical axis is on the natural log scale.

Goodness of fit of study-specific dose–response models

The three tools presented so far can be also used to assess the goodness of fit of the first-stage study-specific dose–response models, if one wishes so. Only minor modifications in the formulae are necessary. In particular, it is sufficient to replace the pooled parameter vector $\hat{\theta}$ with the study-specific parameter vectors $\hat{\beta}_i$ and drop the second-stage design matrix \mathbf{Z}_i .

Let the study-specific decorrelated residuals be

$$\tilde{\mathbf{e}}_i^* = \mathbf{C}_i^{-1} (\mathbf{y}_i - \mathbf{X}_i \hat{\beta}_i) = \mathbf{C}_i^{-1} \tilde{\mathbf{e}}_i.$$

These residuals can be used to construct study-specific decorrelated-residuals-versus-exposure plots.

The deviance for the i -th study-specific dose–response regression model is defined as

$$\tilde{D}_i = (\mathbf{y}_i - \mathbf{X}_i \hat{\beta}_i)^\top \mathbf{S}_i^{-1} (\mathbf{y}_i - \mathbf{X}_i \hat{\beta}_i) = \tilde{\mathbf{e}}_i^\top \mathbf{S}_i^{-1} \tilde{\mathbf{e}}_i,$$

and when the i -th study-specific model is correctly specified, \tilde{D}_i asymptotically follows a chi-square random variable with $J_i - q$ degrees of freedom. Moreover, as the K studies are summed to be independent, it is also possible to set up a joint test for model specification of all the K first-stage study-specific dose–response regressions. In fact, under the null hypothesis that all the first-stage models are correctly specified, the sum of the K study-specific deviances \tilde{D}_i is asymptotically distributed as a chi-square random variable with $\sum_{i=1}^K (J_i - q) = n - Kq$ degrees

of freedom:

$$\tilde{D} = \sum_{i=1}^K \tilde{D}_i = \sum_{i=1}^K \tilde{\mathbf{e}}_i^\top \mathbf{S}_i^{-1} \tilde{\mathbf{e}}_i \sim \chi_{n-Kq}^2. \quad (5.6)$$

Lastly, the coefficient of determination for the i -th study is defined as

$$R_i^2 = 1 - \frac{(\mathbf{y}_i - \mathbf{X}_i \hat{\boldsymbol{\beta}}_i)^\top \mathbf{S}_i^{-1} (\mathbf{y}_i - \mathbf{X}_i \hat{\boldsymbol{\beta}}_i)}{\mathbf{y}_i^\top \mathbf{S}_i^{-1} \mathbf{y}_i}.$$

Relation between D and Q statistics

Analogously to the vector of decorrelated residuals \mathbf{e}_i^* , let the following objects

$$\begin{aligned} \mathbf{y}_i^* &= \mathbf{C}_i^{-1} \mathbf{y}_i \\ \mathbf{X}_i^* &= \mathbf{C}_i^{-1} \mathbf{X}_i, \end{aligned}$$

be the vector of decorrelated non-referent logRRs and the decorrelated design matrix for the i -th study. Suppose also for sake of simplicity that $\mathbf{Z}_i = \mathbf{I}_{(J_i)}$ for $i = 1, \dots, K$.

It is possible to show that the difference between D [equation (5.5)] and Q [equation (2.28)] is equal to \tilde{D} [equation (5.6)]. In fact,

$$\begin{aligned} D &= \sum_{i=1}^K (\mathbf{y}_i - \mathbf{X}_i \hat{\boldsymbol{\theta}})^\top \mathbf{S}_i^{-1} (\mathbf{y}_i - \mathbf{X}_i \hat{\boldsymbol{\theta}}) = \\ &= \sum_{i=1}^K (\mathbf{y}_i^* - \mathbf{X}_i^* \hat{\boldsymbol{\theta}})^\top (\mathbf{y}_i^* - \mathbf{X}_i^* \hat{\boldsymbol{\theta}}) = \\ &= \sum_{i=1}^K (\mathbf{y}_i^{*\top} \mathbf{y}_i^* - \mathbf{y}_i^* \mathbf{X}_i^* \hat{\boldsymbol{\theta}} - \hat{\boldsymbol{\theta}}^\top \mathbf{X}_i^{*\top} \mathbf{y}_i^* - \hat{\boldsymbol{\theta}}^\top \mathbf{X}_i^{*\top} \mathbf{X}_i^* \hat{\boldsymbol{\theta}}) \end{aligned}$$

and

$$\begin{aligned} Q &= \sum_{i=1}^K (\hat{\boldsymbol{\beta}}_i - \hat{\boldsymbol{\theta}})^\top \hat{\mathbf{V}}(\boldsymbol{\beta}_i)^{-1} (\hat{\boldsymbol{\beta}}_i - \hat{\boldsymbol{\theta}}) = \\ &= \sum_{i=1}^K (\hat{\boldsymbol{\beta}}_i - \hat{\boldsymbol{\theta}})^\top \underbrace{(\mathbf{X}_i^\top \mathbf{S}_i^{-1} \mathbf{X}_i)}_{\text{GLS estimator}} (\hat{\boldsymbol{\beta}}_i - \hat{\boldsymbol{\theta}}) = \\ &= \sum_{i=1}^K (\hat{\boldsymbol{\beta}}_i - \hat{\boldsymbol{\theta}})^\top (\mathbf{X}_i^{*\top} \mathbf{X}_i^*) (\hat{\boldsymbol{\beta}}_i - \hat{\boldsymbol{\theta}}) = \\ &= \sum_{i=1}^K (\mathbf{X}_i^* \hat{\boldsymbol{\beta}}_i - \mathbf{X}_i^* \hat{\boldsymbol{\theta}})^\top (\mathbf{X}_i^* \hat{\boldsymbol{\beta}}_i - \mathbf{X}_i^* \hat{\boldsymbol{\theta}}) = \\ &= \sum_{i=1}^K (\mathbf{X}_i^* (\mathbf{X}_i^{*\top} \mathbf{X}_i^*)^{-1} \mathbf{X}_i^{*\top} \mathbf{y}_i^* - \mathbf{X}_i^* \hat{\boldsymbol{\theta}})^\top (\mathbf{X}_i^* (\mathbf{X}_i^{*\top} \mathbf{X}_i^*)^{-1} \mathbf{X}_i^{*\top} \mathbf{y}_i^* - \mathbf{X}_i^* \hat{\boldsymbol{\theta}}) = \end{aligned}$$

$$\begin{aligned}
&= \sum_{i=1}^K (\mathbf{H}_i^* \mathbf{y}_i^* - \mathbf{X}_i^* \hat{\boldsymbol{\theta}})^\top (\mathbf{H}_i^* \mathbf{y}_i^* - \mathbf{X}_i^* \hat{\boldsymbol{\theta}}) = \\
&= \sum_{i=1}^K \left(\underbrace{\mathbf{y}_i^{*\top} \mathbf{H}_i^{*\top} \mathbf{H}_i^* \mathbf{y}_i^*}_{\mathbf{H}_i^* \text{ is idempotent}} - \mathbf{y}_i^* \mathbf{H}_i^{*\top} \mathbf{X}_i^* \hat{\boldsymbol{\theta}} - \hat{\boldsymbol{\theta}}^\top \underbrace{\mathbf{X}_i^{*\top} \mathbf{H}_i^* \mathbf{y}_i^*}_{\mathbf{H}_i^* \text{ is symmetric and } \mathbf{H}_i^* \mathbf{X}_i^* = \mathbf{X}_i^*} + \hat{\boldsymbol{\theta}}^\top \mathbf{X}_i^{*\top} \mathbf{X}_i^* \hat{\boldsymbol{\theta}} \right) = \\
&= \sum_{i=1}^K \left(\mathbf{y}_i^{*\top} \mathbf{H}_i^* \mathbf{y}_i^* - \mathbf{y}_i^* \mathbf{X}_i^* \hat{\boldsymbol{\theta}} - \hat{\boldsymbol{\theta}}^\top \mathbf{X}_i^{*\top} \mathbf{y}_i^* + \hat{\boldsymbol{\theta}}^\top \mathbf{X}_i^{*\top} \mathbf{X}_i^* \hat{\boldsymbol{\theta}} \right).
\end{aligned}$$

The difference between D and Q is therefore

$$\begin{aligned}
D - Q &= \sum_{i=1}^K (\mathbf{y}_i^{*\top} \mathbf{I}_{(J_i)} \mathbf{y}_i^* - \mathbf{y}_i^{*\top} \mathbf{H}_i^* \mathbf{y}_i^*) = \\
&= \sum_{i=1}^K \mathbf{y}_i^{*\top} \underbrace{(\mathbf{I}_{(J_i)} - \mathbf{H}_i^*)}_{\text{symmetric and idempotent}} \mathbf{y}_i^* = \\
&= \sum_{i=1}^K \mathbf{y}_i^{*\top} (\mathbf{I}_{(J_i)} - \mathbf{H}_i^*)^\top (\mathbf{I}_{(J_i)} - \mathbf{H}_i^*) \mathbf{y}_i^* = \\
&= \sum_{i=1}^K \tilde{\mathbf{e}}_i^{*\top} \tilde{\mathbf{e}}_i^* = \\
&= \sum_{i=1}^K \tilde{\mathbf{e}}_i^\top (\mathbf{C}_i^{-1})^\top (\mathbf{C}_i^{-1}) \tilde{\mathbf{e}}_i = \\
&= \sum_{i=1}^K \tilde{\mathbf{e}}_i^\top \mathbf{S}_i^{-1} \tilde{\mathbf{e}}_i = \tilde{D}.
\end{aligned}$$

A direct consequence of this relation is that $D \geq Q$. In particular, $D = Q$ when all the first-stage study-specific regression models fit perfectly the reported logRRs — that is, $R_i^2 = 1$ for every i .

Perhaps not surprisingly at this point, the degrees of freedom of D minus the degrees of freedom of Q is equal to the degrees of freedom of \tilde{D} . In fact

$$n - qm - (Kq - qm) = n - Kq.$$

5.5.2 Goodness of fit assessment: dose–response meta-analysis on body mass index and incidence of localized prostate cancer

To illustrate the 3 tools introduced in the previous section, we will evaluate the goodness of fit of the updated dose–response meta-analysis on BMI and incidence of localized prostate cancer presented in section 5.4.2. This meta-analysis was based on 18 prospective studies for a total of 46 non-referent logRRs.

The identity transformation for BMI — that is, modeling BMI linearly — resulted in a particularly poor goodness of fit (model 1). In particular, the test for model specification

showed evidence of lack of fit, as indicated by a deviance of 64 on $46 - 1 = 45$ degrees of freedom ($p = 0.03$) (table 5.3). The percentage of total variability in the non-referent logRR estimates explained by this model was $R^2 = 29\%$. Furthermore, the decorrelated-residuals-versus-exposure plot showed that the fit of the model was poor. In particular, the decorrelated residuals were mostly positive for low values of the rescaled exposure, while they were almost all negative for high exposure values (figure 5.12, panel A).

The lack of fit of model 1 was addressed by modeling BMI using RCS with 3 knots positioned at the 10th, 50th, and 90th percentiles of the exposure distribution (model 2). The improvement in the goodness of fit of model 2 over model 1 was reflected by the increase in the coefficient of determination (from 29% to 48%) and by the large reduction in the deviance with respect to the difference in the degrees of freedom ($D = 64 - 47 = 17$, $df = 45 - 44 = 1$, $p_{\text{non-linearity}} < 0.001$) (table 5.3). Furthermore, the decorrelated-residuals-versus-exposure plot reflected the improved fit of model 2, especially for the right tail of the exposure distribution (figure 5.12, panel B). Lastly, from the test for model specification, we observed no evidence of lack of fit for model 2 ($D = 47$, $df = 46 - 2 = 44$, $p = 0.35$).

Similar conclusions regarding the goodness of fit of the pooled dose-response curve following a non-linear transformation of the exposure were reached when using the other two transformations proposed in section 5.4.2, namely RCS with 3 knots positioned at the 25th, 50th, and 75th percentiles (model 3), and quadratic polynomial (model 4). A summary of the goodness of fit for the 4 models considered here is reported in table 5.3.

Table 5.3: Goodness of fit measures for the updated dose-response meta-analysis on BMI and incidence of localized prostate cancer presented in section 5.4.2

Model	BMI transformation	Deviance	df	p -value ^a	p -value ^b	R^2	R^2_{adj}
1	Linear (identity)	64	45	0.03	—	29%	29%
2	RCS with 3 knots ^c	47	44	0.35	< 0.001	48%	45%
3	RCS with 3 knots ^d	44	44	0.45	< 0.001	50%	48%
4	Quadratic polynomial	49	44	0.26	< 0.001	45%	42%

^a p -value from the test for model specification.

^b p -value for relative goodness of fit with respect to model 1.

^c Knots positioned at the 10th, 50th, and 90th percentiles of BMI distribution.

^d Knots positioned at the 25th, 50th, and 75th percentiles of BMI distribution.

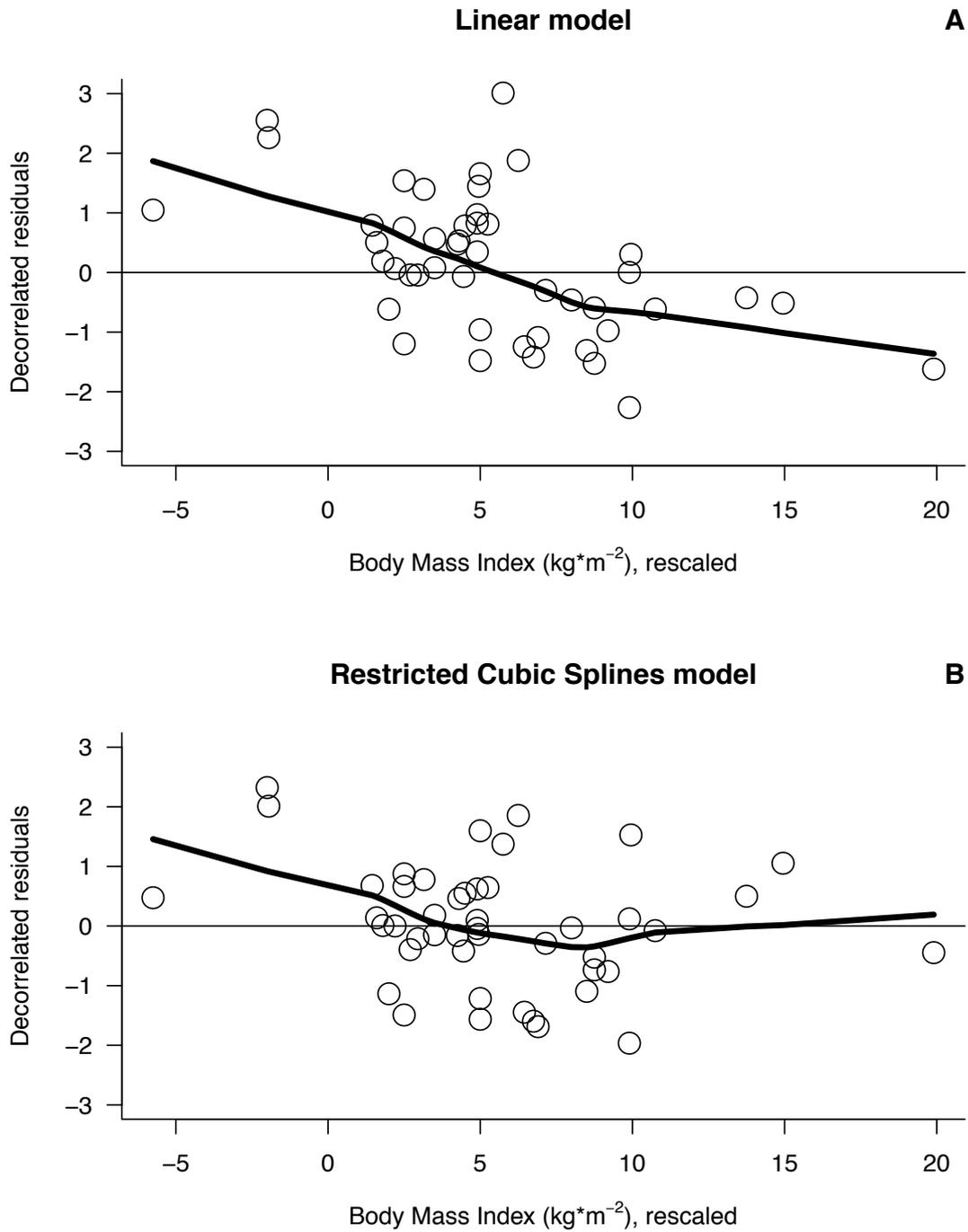


Figure 5.12: Decorrelated residuals (hollow circles) and LOWESS smoother (black line) for model 1 (panel A) and for model 2 (panel B) in the updated dose-response meta-analysis on BMI and incidence of localized prostate cancer presented in section 5.4.2.

Chapter 6

Discussion

6.1 Body mass index and prostate cancer incidence and mortality

6.1.1 Major findings and comparison with literature results

BMI during middle-late adulthood

In Paper I and Paper IV we observed a dual association between BMI during middle-late adulthood and prostate cancer: an increased risk of advanced and fatal prostate cancer, and a decreased risk of localized prostate cancer (comparing overweight and obese men to normal-weight men). These findings support the hypothesis of etiological heterogeneity of prostate cancer in relation to obesity (Discacciati and Wolk, 2014).

In Paper I we observed an inverse-U shaped relation between BMI and incidence of localized prostate cancer. This result was also observed in the updated analyses with a longer follow-up period and, noteworthy, it was robust to different modeling strategies of the exposure. Although no evidence of non-linearity was observed in Paper IV, the updated meta-analysis showed a similar dose-response relation to that reported in Paper I. Furthermore, the effect size estimates were remarkably similar. A lower localized prostate cancer incidence was observed in particular for overweight and obese men as compared with normal-weight men. The decreased incidence for underweight men was much less pronounced.

An increased incidence of advanced prostate cancer was observed both in Paper I and in Paper IV. Results were again consistent, especially considering the updated analyses carried out in this thesis, where a 7–11% increased IR was observed for every 5-unit increment in BMI.

Consistently with the results for advanced prostate cancer, a 12% increased MR was observed for death due to prostate cancer in Paper I. The increased number of cases due to the extended follow-up time contributed in making the estimated MRR slightly more precise. In addition, the worse survival associated with increased BMI levels was also observed when analyzing the percentiles of age at prostate cancer death using quantile regression for censored data.

These results are in line with recent epidemiologic literature. Higher BMI levels were

observed to be associated with lower localized prostate cancer incidence in a large dose–response meta-analysis, where a non-linear relation was observed (WCRF and AICR, 2014). Interestingly, an inverse–U shaped association between BMI and the incidence of total prostate cancer was also found in a very large population-based cohort study of 5.24 million adults in the United Kingdom (Bhaskaran et al., 2014). Although the analyses were not carried out by specific subtypes of prostate cancer, one might speculate that the presumably high proportion of localized cases conferred to the association an inverse–U shape.

BMI was positively linearly associated with advanced prostate cancer in many, but not all, of the cohort studies that we included in the meta-analysis, as shown in figure A.4. However, the results from a recent dose–response meta-analysis of 24 cohort studies are in agreement with our findings (WCRF and AICR, 2014). Comparable results were also observed in a “high versus low” meta-analysis (Zhang et al., 2015).

Lastly, a positive association between BMI and prostate cancer mortality, similar in magnitude to what we observed in the COSM, was reported in a dose–response meta-analysis of 6 population-based cohort studies [RR for every 5-unit increment in BMI: 1.15 (95% CI: 1.06–1.25)] (Cao and Ma, 2011). A large study, not included in the aforementioned meta-analysis, also observed a positive association between BMI and prostate cancer MR (Häggström et al., 2012). Consistently with these findings, BMI was observed to be associated with a higher IR of biochemical recurrence (Bassett et al., 2005; Strom et al., 2005, 2006; Efstathiou et al., 2007b; Palma et al., 2007; Ly et al., 2010; Cao and Ma, 2011) and with a higher rate of prostate cancer–specific mortality in many (Efstathiou et al., 2007a; Gong et al., 2007; Ma et al., 2008; Cao and Ma, 2011; Cantarutti et al., 2015), but not all studies (Bonn et al., 2014).

BMI during early adulthood

In Paper I, no evidence of an association between BMI during early adulthood and incidence of localized prostate cancer was observed. This lack of evidence remained also after extending the follow-up until 31 December 2011. Although we observed inverse associations between BMI at age 30 years and the risk of advanced and fatal prostate cancer, these results were very weak.

Comparison of these results with other studies is complicated due to the heterogeneity in the time window considered for the exposure (Robinson et al., 2008; Sutcliffe and Colditz, 2013). A systematic review and dose–response meta-analysis of 16 studies on BMI measured at 18–29 years of age and total prostate cancer observed a 6% increased risk for every 5-unit increment in early-adult BMI [RR: 1.06 (95% CI: 0.99–1.14)] (Robinson et al., 2008). In particular, the pooled RR for the 5 studies reporting BMI during the ages 25–29 years was equal to 1.14 (95% CI: 1.00–1.30), in contrast with our findings. Studies analyzing BMI ‘during college’ age and ‘during the twenties’ reported weaker associations.

Only a few studies investigated the association between BMI during early adulthood by subtype of the disease. For localized prostate cancer, findings were inconsistent (Schuurman et al., 2000; Littman et al., 2007; Wright et al., 2007). Similarly, results for advanced prostate

cancer were heterogeneous, ranging from inverse (Möller et al., 2015) to direct associations (Schuurman et al., 2000; Dal Maso et al., 2004). However, the majority of the studies reported very little evidence of an association (Giles et al., 2003; Robinson et al., 2005; Littman et al., 2007; Wright et al., 2007; Möller et al., 2013). Not surprisingly, these inconsistent results were also observed for prostate cancer mortality (Wright et al., 2007; Burton et al., 2010; Möller et al., 2013, 2015).

6.1.2 Biological mechanisms

BMI during middle-late adulthood

Possible biological mechanisms that could explain the associations between BMI and prostate cancer incidence and mortality observed in Paper I and Paper IV are still partially unclear. However, three pathways in particular have been proposed in the literature: the insulin/insulin-like growth factor 1 (IGF-1), the sex hormones, and the inflammation pathway (Wirén and Stattin, 2008; Roberts et al., 2010; Renehan et al., 2015).

First, obesity is associated with hyperinsulinemia which in turn, due to decreased levels of IGF-binding proteins 1 and 2, increases the circulating amounts of bioactive IGF-1 (Nam et al., 1997), a growth factor with a pathogenic role in many cancers (Roberts et al., 2010). High levels of IGF-1, in particular, have been associated with increased prostate cancer incidence in 2 meta-analyses (Renehan et al., 2004; Rowlands et al., 2009) and in a large pooling project of 12 prospective studies (Roddam et al., 2008). However, a shortcoming of this explanation is that mean IGF-1 levels have been observed to be non-linearly associated with BMI, peaking at 24–26 kg × m⁻² (Yamamoto and Kato, 1993; Lukanova et al., 2002). Interestingly, this was roughly the BMI range where the highest incidence of localized prostate cancer was observed in Paper I (figure 5.2) and in the updated dose–response meta-analysis (figure 5.9).

Second, obesity is linked with decreased androgen levels (Lima et al., 2000). No evidence of an association between androgens and incidence of total prostate cancer was observed in a large collaborative analysis of 18 prospective studies (Endogenous Hormones and Prostate Cancer Collaborative Group et al., 2008). At the same time, in line with our findings, lower concentrations of free testosterone were observed to be linked with a decreased incidence of non-aggressive well-differentiated prostate cancer and with an increased incidence of aggressive low-differentiated prostate cancer in two prospective cohort studies (Platz et al., 2005; Severi et al., 2006). Furthermore, it has been observed that, among men diagnosed with prostate cancer, those with lower testosterone levels have a higher prevalence of the aggressive phenotype (Hoffman et al., 2000; Schatzl et al., 2001; D'Amico et al., 2002; Massengill et al., 2003; Schnoeller et al., 2013). It has been therefore speculated that low testosterone levels may promote the development of aggressive prostate cancer (Hsing et al., 2007; Freedland and Platz, 2007). Lastly, in the PCPT it was observed that finasteride, a drug that lowers dihydrotestosterone levels, decreased overall prostate cancer risk, but at the same time it increased the risk of high-grade tumors (Gleason score 7–10) (Thompson et al., 2003). In the long-term analyses with 18 years of follow-up, finasteride was again observed to reduce the

risk of prostate cancer (Thompson et al., 2013). This reduction was entirely due to fewer low-grade tumors (Gleason score 2–6), as high-grade prostate cancers were still more common in the finasteride arm. The relative increase of high-grade tumors, however, decreased from 27% in the primary study to 17% in the long-term study.

Third, obesity is a state of chronic inflammation mediated through altered levels of adipokines, such as leptin (a potent inflammatory agent) or adiponectin (an anti-inflammatory adipokine). Leptin, which is elevated in obesity, has been observed to have a pro-tumor potential *in vitro* (Somasundar et al., 2004), but epidemiologic studies observed no evidence of an association with prostate cancer risk or tumor stage at prostatectomy (Freedland et al., 2005; Baillargeon et al., 2006; Li et al., 2010). Conversely, adiponectin has anti-tumor properties and its serum levels are decreased in obese individuals (Freedland et al., 2010; Dalamaga et al., 2012). Adiponectin has been found to be inversely associated with metastatic prostate cancer incidence and mortality (Li et al., 2010). Moreover, adiponectin levels have been observed to be inversely associated with tumor's histologic grade and disease stage among men diagnosed with prostate cancer (Goktas et al., 2005).

BMI during early adulthood

The physiologic changes during the developmental stages of the prostate and immediately thereafter — when the prostate may be more susceptible to endogenous and exogenous carcinogenic exposures — may play an important role in tumor initiation and development (Hsing, 1996; Giovannucci et al., 1997; Sutcliffe and Colditz, 2013). However, the biologic mechanisms that may explain a possible link between prostate cancer risk and obesity during childhood, puberty and early adulthood are unclear.

Adiposity during early life and adolescence, which has been observed to often persist during adulthood (The et al., 2010), has been found to be associated with delayed pubertal development in boys (Wang, 2002). Due to the fact that puberty is associated with a steep increase in IGF-1 levels (Keenan et al., 1993; Juul et al., 1994), a delayed pubertal development could, in theory, lead to a lower cumulative exposure to IGF-1 and/or a lower exposure during those ages that are crucial for prostate development. In addition, obesity during earlier stages of life is linked with later diabetes incidence, which in turn has been consistently observed to be inversely associated with the risk of prostate cancer (Jian Gang et al., 2015).

These speculative biological mechanisms could partially explain the inverse association that we observed between BMI at age 30 years and incidence of advanced prostate cancer and prostate cancer mortality.

6.1.3 Detection bias

There is a number of factors that could make prostate cancer detection more difficult in obese men. This relationship between body adiposity and detection sensitivity could lead to an apparent 'effect modification' by aggressiveness of the disease at diagnosis (Garcia-Closas and Berrington de Gonzalez, 2015). Therefore, the heterogeneity in the association between BMI

during middle-late adulthood and the incidence of prostate cancer by subtype of the disease might have non-causal explanations.

First, obese men have lower mean PSA values (Bañez et al., 2007), which in turns leads to a reduction in the rate of PSA-driven biopsies. The reason why obese men have lower PSA levels on average is still unclear. One explanation is that obese men have lower testosterone levels, leading to less PSA production. It has also been hypothesized that this is due to increased blood volume in obese subjects causing PSA hemodilution, since no evidence of an association between mean PSA mass and BMI was observed in some studies (Bañez et al., 2007; Grubb et al., 2009).

Second, a thorough digital rectal examination is more difficult in obese men and its predictive value in prostate cancer detection has been observed to be modified by obesity (Chu et al., 2011), which could result in missed cancers.

Third, several studies have suggested that obese men have larger prostates on average (Dahle et al., 2002; Freedland et al., 2006b), which reduces the likelihood of finding cancer at biopsy (Freedland et al., 2006b). Furthermore, most prostate cancers detected by PSA screening are very small and they cannot be visualized with conventional imaging, making prostate biopsy “analogous to looking for a needle in a haystack” (Buschemeyer and Freedland, 2007). Therefore, prostatic enlargement in obese men would make biopsy detection even more complicated, all other things being equal (Kranse et al., 1999).

All these factors combined could potentially allow prostate cancer growth to continue undetected. This would eventually result in a higher occurrence of advanced disease in obese men as compared with normal-weight men and, at the same time, in a lower occurrence of localized disease.

To what extent detection bias explains the results reported in epidemiologic studies, including ours, it is unknown. However, even in the pre-PSA era obesity was positively associated with prostate cancer mortality (Rodriguez et al., 2001). Furthermore, obesity has been observed to be associated with decreased odds of low-grade prostate cancer and, at the same time, increased odds of high-grade prostate cancer even when all men underwent biopsy (Gong et al., 2006). Detection bias is therefore unlikely to fully explain the association between BMI and prostate cancer mortality, and the subtype-specific associations with prostate cancer incidence.

Lastly, in our data we observed no evidence of heterogeneity in the associations by county of enrollment (table 5.1).²⁷ Although this analysis is obviously sub-optimal — men enrolled in one county may have in fact moved somewhere else during the follow-up time — it provides no evidence in support of the hypothesis that the observed associations are due to detection bias.

²⁷County of enrollment reflected possible different degrees of PSA-screening uptake. See section 4.3.1.

6.1.4 Body mass index as surrogate of obesity

The usage of BMI as a proxy for obesity — “a condition characterized by the excessive accumulation and storage of fat in the body”²⁸ — has some limitations. At the same time, thanks to its simplicity and cost-effectiveness, BMI is likely the most commonly used measure of obesity in large-scale epidemiologic studies (Michels et al., 1998).

The major shortcoming of this measure is probably that single individuals’ specific composition and body shape do not enter into BMI calculations. For example, very muscular men with little body fat can have a high BMI, which would be wrongly interpreted as an indication of obesity. However, these types of men arguably constitute a limited proportion of the men enrolled in most studies, with an exception possibly being the Swedish Construction Workers cohort (Stocks et al., 2010), which was included in the meta-analysis of Paper IV.

Although BMI may be inadequate to measure body adiposity for a single subject, it remains a reasonably accurate measure of body adiposity in populations (Flegal et al., 2009). However, a systematic tendency to over-report height and under-report weight, resulting in BMI being biased downwards, has been repeatedly observed (Connor Gorber et al., 2007). Perhaps not surprisingly, this tendency to under-report weight has been observed to be more common among overweight and obese individual than among normal-weight individuals (Boström and Diderichsen, 1997; Kovalchik, 2009).

The consequences of this measurement error depend on the “true” unknown underlying association that is being examined. For example, for advanced and fatal prostate cancer risk — assuming that the “true” association with BMI during middle-late adulthood is positive — a systematic under-reporting of BMI in obese men would lead to attenuated associations (RRs closer to the unity).

6.2 Survival percentiles when age at the event is the relevant time scale

When describing survival data from observational epidemiologic studies, the standard approach is to focus on the hazard function, while differences in survival between groups of individuals are usually summarized by means of HRRs. The reason for the ubiquitous presence of HRRs in the epidemiologic literature is arguably due to the wide availability of statistical tools to directly model the hazard as a function of some covariates of interest, and not to the fact that HRRs are inherently “better” measures of association than others (Hernán, 2010; Uno et al., 2014).

A different approach to describe survival data consists in focusing on survival percentiles, which thoroughly describe the distribution of survival time. Survival percentiles provide the link between the proportion of study subjects that has experienced the event of interest and the time by which that proportion is reached.

²⁸<http://www.merriam-webster.com/dictionary/obesity>

As survival percentiles can be obtained from survival curves, both hazard models and the Kaplan-Meier estimator can be utilized to “indirectly” estimate them.²⁹ As seen in section 2.2.2, however, calculating survival curves following PH models can sometimes give a “misleading impression” (Kalbfleisch and Prentice, 2002) and is impractical if one wants to relax the PH assumption by employing time-dependent coefficients. Moreover, calculation of confidence intervals for survival percentiles obtained in this way is not straightforward (Burr, 1994; Lai and Su, 2006). The Kaplan-Meier estimator, on the other hand, is often inadequate in the context of observational epidemiology, where modeling is generally preferred over simple stratification.

Quantile regression for censored data, on the other hand, focuses directly on survival percentiles posing no restrictions on the shape of the survival function and offers all those advantages of statistical modeling that are so important in the analysis of observational data.

In Paper II, we proposed an intuitive and simple approach to extend the use of Laplace regression to those situations in which investigators want to use age as the underlying time scale. We showed that delayed entries, introduced by the change in the time scale, complicate the interpretation of survival percentiles obtained from survival curves. In fact, in the presence of delayed entries, it is no longer true that the $100p$ -th percentile of attained age, say $a(p)$, can be interpreted as the age by which $100p\%$ of the study population has experienced the event of interest. It may even occur, for example, that by age $a(p)$ less than $100p\%$ of study participants have been enrolled in the study.

By conditioning the quantile regression model on age at entry (baseline age), the $100p$ -th survival percentile of age at the event can now be interpreted as the age by which $100p\%$ of the study participants have experienced the event, given a fixed baseline age. Moreover, the model coefficients express the difference in the $100p$ -th percentile of age at the event between exposed and unexposed individuals, always conditional on baseline age. We think that this extension can be particularly useful for the analysis of observational studies, where attained age is often a more meaningful and natural time scale than time elapsed since some arbitrary baseline event.

As previously written, survival percentiles thoroughly describe the distribution of survival time, and likewise PDs give a full picture of the differences in the distribution of age-at-event between exposed and unexposed individuals. This can be, however, a double-edged sword. In fact, unless one is interested in a pre-specified PD (as it could be the case for clinical trials), the richer picture provided by PDs also requires more information to be reported (in terms of figures, words and/or numbers). Focusing on one single arbitrary chosen PD can give a “misleading impression” of the association just like reporting one single HRR when the PH does not seem to hold. In the illustrative example in Paper II, we reported differences in the 25th, 50th, and 75th percentiles of age at death according to smoking status for this reason.

²⁹The word “indirectly” is used to highlight the fact that, both in the case of hazard models and Kaplan-Meier estimator, what is actually being estimated are survival probabilities given study time.

Laplace regression

Among the different available methods for quantile regression for censored data, in this thesis and in Paper II, we employed Laplace regression, whose principal characteristic is probably the Laplacian distributional assumption of the error term. This assumption is shared by other methods for quantile regression (Liu and Bottai, 2009; Farcomeni, 2010; Lee and Neocleous, 2010; Yuan and Yin, 2010). Other proposed techniques do not make distributional assumptions on the error term but are subject to other assumptions, such as global linearity (Portnoy, 2003; Peng and Huang, 2008), not required by Laplace regression. The method by Wang and Wang (2009) overcomes the global-linearity assumption but its computational algorithm requires subjectively setting a smoothing function, which may ultimately have an impact on inference.

Laplace regression has been observed to be robust to violations of the Laplacian distributional assumption. In simulation studies where the error term was generated from a number of different distributions — including normal, lognormal, Student's t , and exponential distribution — the performances of the Laplace estimator in terms of bias and coverage were observed to be remarkably good, even at high quantiles and with large rates of censoring (Bottai and Zhang, 2010, 2011; Bottai and Orsini, 2013; Bottai et al., 2015).

6.3 Risk and rate advancement periods

RAP reflects the exposure impact in the timing of the disease occurrence. For rates, RAP quantifies how much sooner e_1 -exposed individuals reach the same IR of a certain disease as e_0 -exposed individuals, under the assumptions of a monotonically increasing age-disease association and disease-free survival to baseline age.

The fact that RAP is a time-based measure of exposure impact makes it very appealing in risk communication. For example, in a recent paper published in the *British Medical Journal*, Mons et al. (2015) wrote that “risk communication is [...] crucial [...] and risk advancement periods could be easier to grasp for the general public than other epidemiologic risk measures such as relative risks of years of life lost”. Whether this is actually true or not remains to be seen, as no empirical evidence on the usefulness of RAP in risk communication with lay audiences has been collected yet.

What we have observed, however, is the fact that correct interpretation of RAP has eluded many of the studies that have employed this measure so far. In particular, we have identified three major conceptual problems. First, equating RAP with the difference in mean survival time; second, interpreting RAP as the time by which the survival curve for the e_1 -exposed individuals is shifted with respect to the survival curve for the e_0 -exposed individuals; third, equating the RAP concept to that of RRs. Furthermore, we have highlighted a too often neglected statistical problem, which is the high sensitivity of RAP estimates to the form of the age-disease association. All these problems can be quite serious in realistic examples.

The reason why RAP has been repeatedly misinterpreted in the literature is most likely multi-factorial, but a possible explanation is that RAP is a measure involving three variables

(exposure, baseline age, and binary outcome) instead of two as traditional measures of association. As RAP evaluates the impact of the exposure on the relation of age to the outcome, it is more similar to an interaction measure than to a measure of association, although it is not equivalent to a product term in the model. This supplementary complexity might partially explain why RAP has been repeatedly misinterpreted.

RAP in prostate cancer epidemiology

A crucial assumption for sensible use of RAP is that the rate of the outcome strictly increases with age, given exposure and confounders. If this assumption is not met, one should avoid use of RAP. As seen in the COSM (figure 4.1) and in other populations (Ferlay et al., 2015), the incidence of prostate cancer increases until around 70–74 years of age and declines thereafter. This is likely due to less use of PSA-testing in men over 80 years of age (Williams et al., 2011) and, at the same time, to a constant increase over time in PSA-testing among younger men (Salinas et al., 2014). Although the reasons behind the non-monotonicity of the age-incidence curve are unlikely to be biological, this limits the application of RAP in this context. A possible solution is to restrict RAP analysis to men younger than 70–74 years of age to ensure that the assumption of a monotonic increase in disease rate over age holds.

In contrast, the monotonicity assumption seems to hold for prostate cancer mortality (Ferlay et al., 2015). In the example reported in section 5.3.3 using data from the COSM, obese men were observed to experience the same prostate cancer MR over the follow-up period 1998–2012 as that of normal-weight men who were 18 months older at baseline. Despite the lack of evidence of a non-linear association between age and log-mortality rate of prostate cancer, RAP estimates were somewhat sensitive to the functional form with which baseline age entered into the model.

Lastly, interpretation of RAP as the time period by which attainment of a particular rate level can be postponed by eliminating the exposure requires the (conditional) independence of the study disease from competing events. As Brenner et al. (1993) wrote “this limitation is negligible if the RAP is derived for young and middle-aged individuals and if the RAP is not too long”. In the case of prostate cancer mortality, on the other hand, since the vast majority of men dying of the disease are elderly, interpretation of RAP estimates becomes more theoretical.

6.4 Goodness of fit assessment in dose–response meta-analysis

6.4.1 Why goodness of fit assessment is important

Statistical modeling in the context of dose–response meta-analysis can be thought of as ‘descriptive modeling’ (Rosenthal and Rubin, 1985; Shmueli, 2010). Citing the words by Shmueli (2010) “this type of modeling is aimed at summarizing or representing the data structure in a compact manner”.

In order to give a fair representation of the data structure — that is, of the information regarding a certain dose-risk relation — one should make sure that the posited dose–response

meta-analysis models actually provide an adequate description of the data at hand. Therefore, we argue that the natural ‘third stage’ of a dose–response meta-analysis should be the evaluation of its goodness of fit, which can be done in practice by measuring the degree of agreement between fitted and observed data.

A poor fit can raise doubts about the ability of a certain model to summarize the available data or as Greenland (1994) put it “if one views statistical estimates as data summaries, then one can view significant lack of fit as a warning that the fitted model structure and model-based estimates are poor data summaries”.

Despite its importance, however, the issue of how to evaluate goodness of fit of dose–response meta-analysis models has, to the best of our knowledge, never been specifically addressed. As a consequence, assessment of the goodness of fit is rarely, if ever, carried out in practice. As Sutton and Higgins (2008) pointed out “little formal assessment of the goodness-of-fit of meta-analysis models to the data is carried out. This may be partly because many non-statisticians conduct meta-analysis, and to such applied researchers meta-analysis may be seen as a necessary data-processing procedure rather than a model-fitting exercise”.

The aforementioned degree of agreement has been sometimes evaluated by simply overlaying the study-specific RRs to the pooled dose–response curve (see, for example, WCRF and AICR, 2014; Liao et al., 2015). However, although praiseworthy, this approach can be highly misleading as the correlation among the reported logRRs means that even a well-fitting dose–response curve might not pass through the data points. This was clearly illustrated, in the simple case of trend estimation for one single study, in figure 5.11.

Furthermore, study-specific dose–response relations are sometimes illustrated by plotting the reported RRs at their assigned doses and connecting them with straight lines (segments) (WCRF and AICR, 2014). This can be misleading for the very same reasons given above. In fact, visually inferring the dose–response relation from this kind of plot may lead to wrong conclusions, given the that the correlation between RRs is not taken into account.

A digression on goodness of fit

The statistical modeling carried out for the description of COSM data and for the comparison with Swedish national data (section 4.3) can also be viewed as descriptive modeling and the same considerations about goodness of fit apply. In fact, we overlaid to the model predictions the observed (summarized) data, so that the goodness of fit of the models could be, at least qualitatively, evaluated.

Statistical modeling in Paper I, on the other hand, was aimed at ‘explaining’ — that is, testing hypotheses about theoretical constructs (Shmueli, 2010). In ‘explanatory modeling’ one is not usually interested in assessing the overall absolute goodness of fit of a model, as “the fit of the model must be evaluated only against the specific part of the variation [of the outcome] which is relevant to the subset of effects of interest. An overall test of the model fit is too general for this purpose and does not answer the right question” (Hagquist and Stenbeck, 1998).

6.4.2 Deviance, coefficient of determination, and visual assessment

To highlight the need of assessing the goodness of fit in dose–response meta-analysis, we presented and discussed in Paper V three goodness of fit tools (deviance, coefficient of determination, and decorrelated-residuals–versus–exposure plot). These tools can be useful for testing, quantifying, and visually displaying the fit of dose–response meta-analysis models while taking into account the correlation structure of the study-specific logRRs.

The examples given in Paper V and in section 5.5.2 showed how these tools can give important indications regarding the fit of the candidate models. In particular, these tools can help identify dose–response patterns, investigate sources of heterogeneity, and eventually assess whether the pooled dose–response association adequately summarizes the published results. Their use can strengthen the conclusion drawn from a dose–response meta-analysis or, conversely, raise doubts about its ability to describe in an adequate manner the available evidence. However, one should also be aware that these tools come with some limitations.

Limitations and caveats

First, while a small p -value from the test for model specification (deviance) is an indication that the considered model fails at explaining the observed variation in the reported logRRs, a large p -value shall not lead to the conclusion that the model adequately explains all the observed variability. Moreover, although a small p -value is an indication that the tested model is unsatisfactory and needs to be modified (or completely replaced), it provides no indication as to how to proceed. Lastly, a major drawback of all global tests of fit is their low power to detect problems in the model (Hosmer et al., 1997).

Second, when the dose–response meta-analysis models are specified in a data-dependent fashion (also known as data dredging), p -values from the global goodness of fit cannot be formally regarded as valid.

Third, although a $R^2 = 1$ does correspond to a perfect fit, interpreting a low coefficient of determination is more complicated. In fact, R^2 can be close to 0 because of different reasons: the model fits poorly the data, the exposure and the logRRs are not associated, or simply — even under the “correct” model — the GRSS is close to the GTSS.

Fourth, the interpretation of the decorrelated-residuals–versus–exposure plot is based on the visual recognition of patterns in the distribution of the decorrelated residuals by levels of the exposure, which is a subjective experience (Greenland, 1994). In the extreme situation of sparse data, the meta-analyst can “recognize” almost any pattern in the plot.

In conclusion, a good fit alone does not imply that the “correct” model has been selected. In extreme cases, especially when the number of data points is small, very different pooled dose–response curves may appear to be equally satisfactory from a goodness-of-fit point of view. This is not surprising, as it simply reflects the fact that the total amount of available information is limited. In such cases, subject matter knowledge — that is, prior information — will play a crucial role in selecting the final model. At the same time, goodness of fit assessment can help to weed out those models that fail at adequately summarizing the available evidence.

Chapter 7

Conclusions

The results presented in this thesis contribute to the body of scientific evidence regarding the association between BMI during early and middle-late adulthood and prostate cancer incidence and mortality. Furthermore, this thesis contributes to the advancement of the epidemiologic field by extending the use of quantile regression for censored data to those situations where attained age is the time scale of interest, by clarifying the appropriate use and interpretation of RAP, and by proposing useful and relevant methods to assess the goodness of fit of dose–response models in research synthesis.

More specifically we conclude the following:

- In a large population-based cohort of Swedish men, BMI measured during middle-late adulthood was inversely associated with the incidence of localized prostate cancer. At the same time, BMI was directly associated with the incidence of advanced prostate cancer and with prostate cancer mortality. BMI during early adulthood was only weakly inversely associated with the incidence of advanced prostate cancer and with prostate cancer mortality (Paper I).
- Similar results regarding the dual dose–response association between BMI during middle-late adulthood and the incidence of localized and advanced prostate cancer were observed by summarizing the published epidemiologic evidence. This supports the hypothesis of etiological heterogeneity of prostate cancer in relation to obesity during middle-late adulthood (Paper IV).
- The use of quantile regression for censored data can be extended to those situations where the time scale of interest is attained age at the event instead of follow-up time. In particular, in the presence of delayed entries, Laplace regression can be used to model percentiles of age at the event by conditioning on baseline age (Paper II).
- The misconceptions appeared in the literature radically changed the meaning of RAP. Moreover, we showed how this measure is extremely sensitive to the form of the age–disease dependence in the rate or risk model. As a result, RAP can make more harm than good if misinterpreted or estimated from misspecified models (Paper III).

- Goodness of fit of dose–response meta-analysis models should be routinely assessed. The tools illustrated in this thesis prove useful to test, quantify, and visually display the fit of dose–response meta-analysis models, while taking into account the correlation structure of the study-specific logRRs (Paper V).

Chapter 8

Future research

Based on the conclusions presented in this thesis, future research includes:

- Further investigating the role on prostate cancer incidence and mortality of obesity measured at different time points in life. Cohort studies of children, adolescents, or young adults initiated decades ago could for example provide invaluable data to elucidate these associations. Furthermore, linkage of cross-sectional or cohort data collected decades ago with cancer registries could be another viable short-term option. Records of children's weight collected at school or military enlistment registries (military service was mandatory in Sweden between 1901 and 2010) could provide unique data on anthropometric measurements.
- More in general, body fatness and changes in body weight over the life course in relation to prostate cancer risk deserve additional investigation. This requires well-designed prospective studies of prostate cancer-free men followed to diagnosis and to death. Availability of repeated measurements is essential to be able to answer this question. Moreover, differences between weight gain/loss around the time of diagnosis and long-term weight gain/loss should be considered when focusing on prostate cancer mortality. Lastly, one should be able to distinguish between intentional and unintentional weight loss. Data from the COSM, thanks to the self-reported weight measurements at two time points (1997 and 2008), could help answering some of these research questions.
- Evaluating the role played by detection bias and other alternative explanations to biological mechanisms in the association between obesity and incidence of localized and advanced prostate cancer.
- Extending the use of survival percentiles to measures that assess the public health impact of an exposure. For example, one could think of a percentile-based measure analogous to the excess fraction (Greenland and Rothman, 2008), where a given PD is recalculated as a fraction of the survival percentile among the exposed.
- Regression methods for measures of disease occurrence based on survival percentiles, such as the geometric rate regression model (Bottai, 2015), merit further attention both

from an applied and methodological point of view.

- Extending and applying additive models (Buja et al., 1989) to dose–response meta-analysis. This would provide a flexible tool to investigate the shape of the dose-risk relation. Formulae for fitting additive models by penalized least squares need to be modified to take into account the correlation structure of the error term and the lack of the intercept. Additive models can be used together with the one-stage meta-analysis approach (see Paper V).
- Developing a point-wise average approach for dose–response meta-analysis, extending the work carried out by Sauerbrei and Royston (2011) on meta-analysis of individual patient data. One of the possible advantages that this approach would give is that the exposure transformation is not constrained to be the same across all the individual studies, as it is the case in the two-stage approach presented in this thesis.
- As a next step following the goodness of fit tools introduced in Paper V, it would be valuable to develop outlier and influence diagnostics for dose–response meta-analysis. These diagnostic tools would prove useful in sensitivity analyses to assess robustness and stability of dose–response meta-analysis models.

Appendix A

Supplementary figures

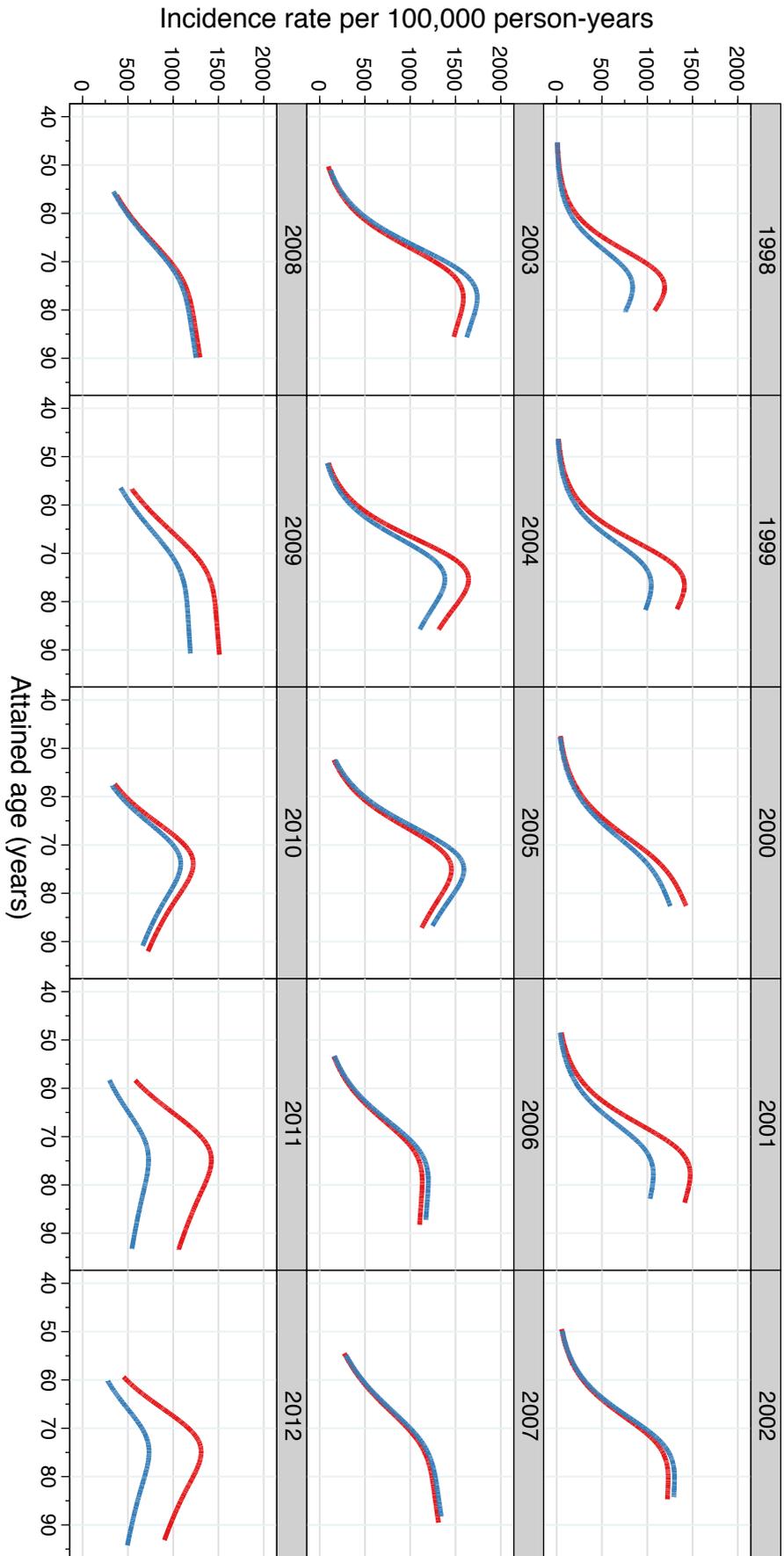


Figure A.1: Incidence rate of prostate cancer in the COSM, conditional on calendar year, attained age, and enrollment county (Västmanland/Örebro). The red line is the model-based predicted incidence rate for Västmanland county. The blue line is the model-based predicted incidence rate for Örebro county. The IRs between the 2 counties are forced to be proportional within calendar year. The $P_{\text{heterogeneity}}$ of the $IRR_{\text{Västmanland vs. Örebro}}$ by calendar year was less than 0.001.

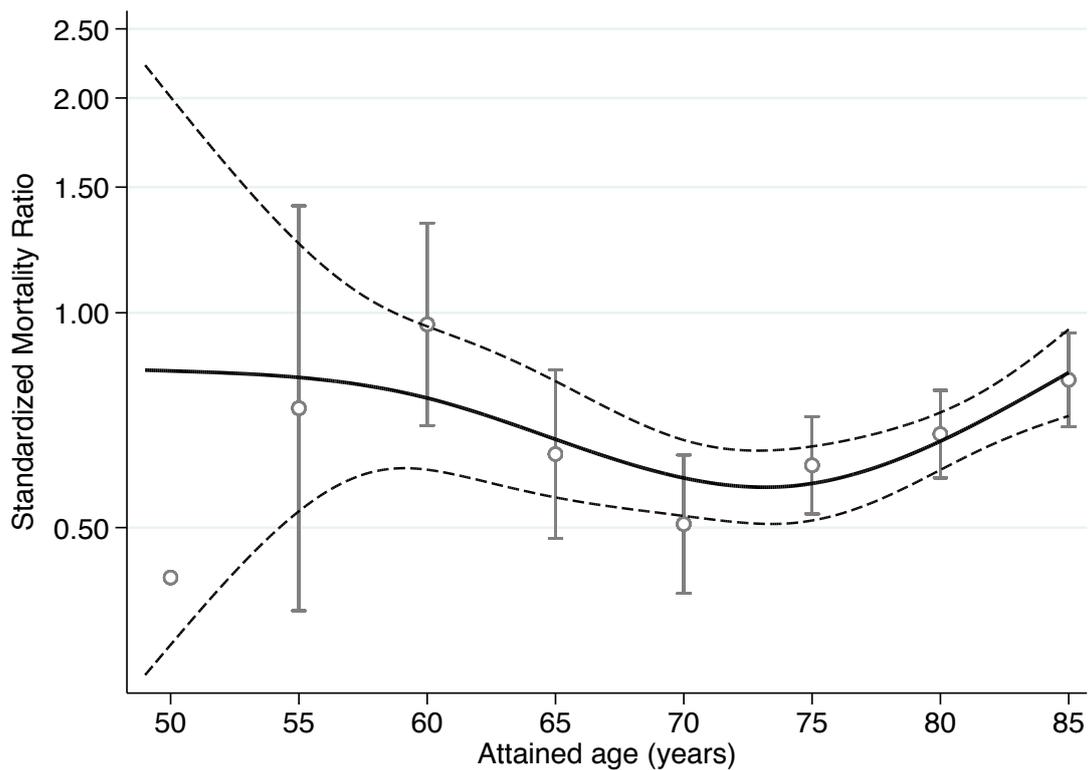


Figure A.2: SMRs of prostate cancer by attained age. The solid line is the model-based predicted SMR, while dashed lines are 95% confidence intervals. The hollow circles represent the observed SMRs by 5-year categories of attained age together with 95% confidence intervals. The confidence interval for $SMR_{2,}$ was not displayed since extremely wide, as it was based on 1 death only. Moreover, given that no deaths were observed in the category 45–49 years of attained age, the graph starts at age 50 years (see Table B.2). The vertical axis is on the natural log scale.

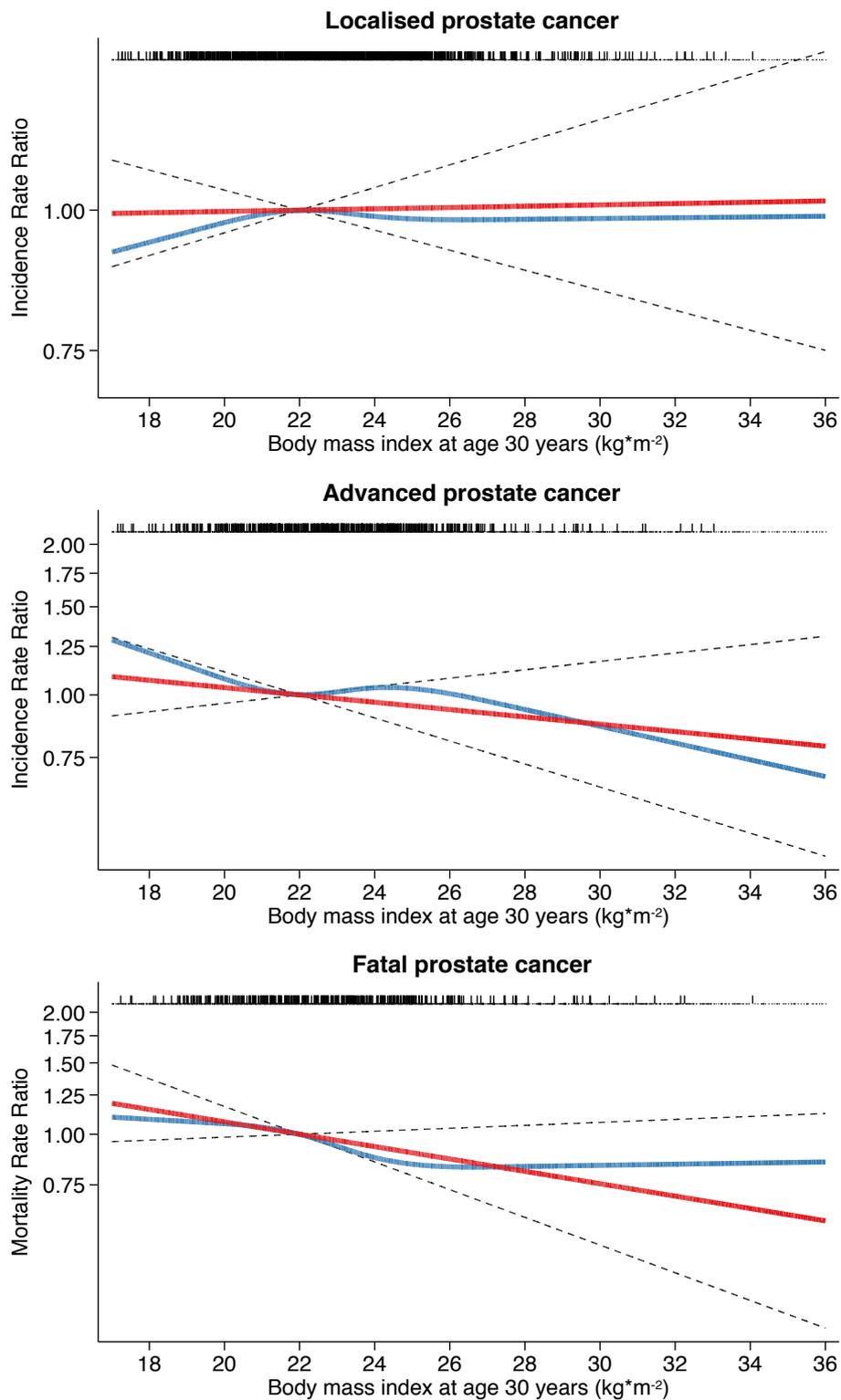


Figure A.3: Multivariable-adjusted associations of BMI at age 30 years ($\text{kg}\cdot\text{m}^{-2}$) with IR of localized and advanced prostate cancer, and with MR of fatal prostate cancer in the updated analysis of Paper I. BMI was modeled using RCS with 4 knots (blue line) and linearly (red line). The referent value was set at $22 \text{ kg}\cdot\text{m}^{-2}$. Vertical lines above the curves represent cases of prostate cancer. The vertical axes are on the natural log scale.

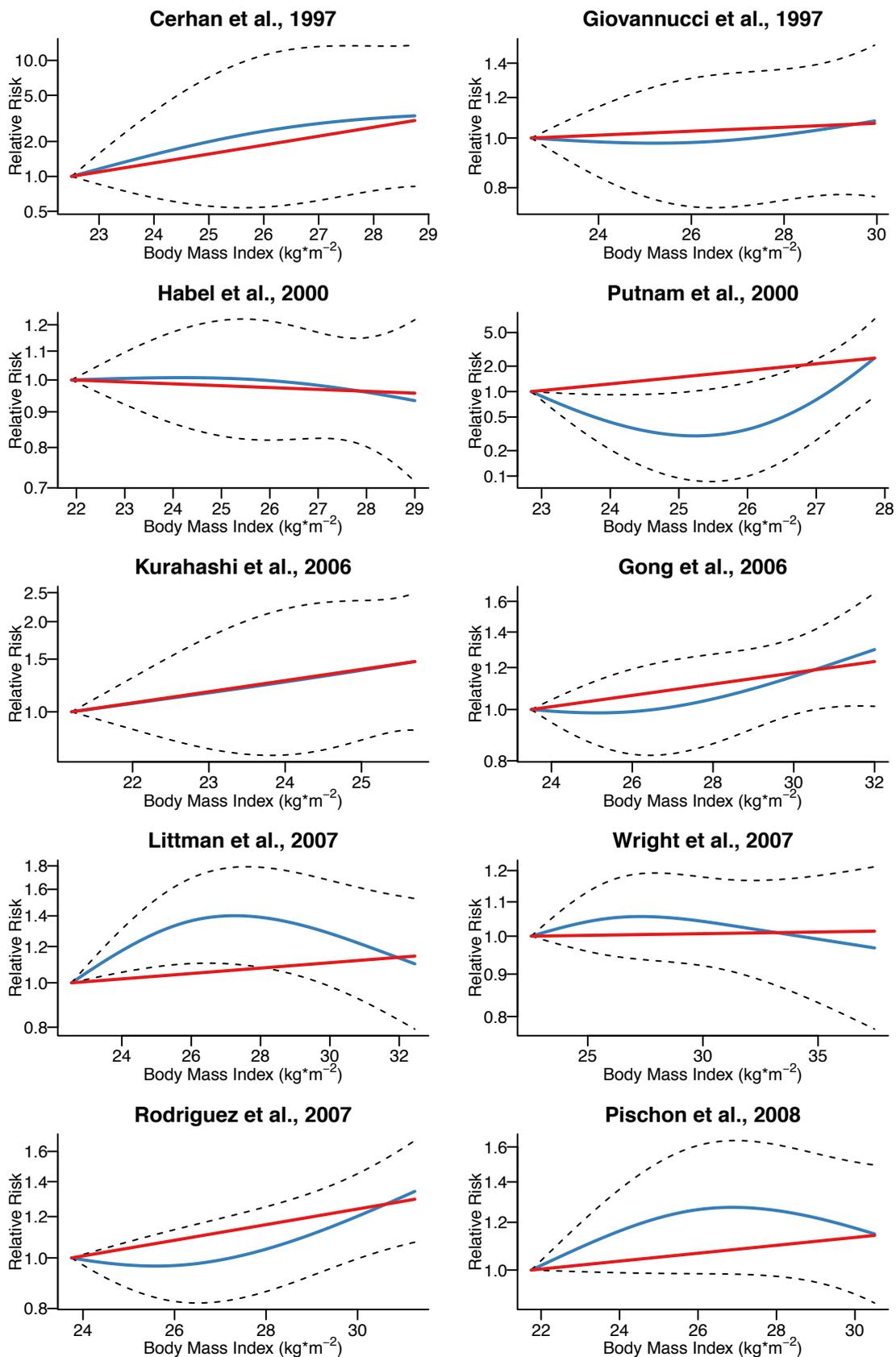
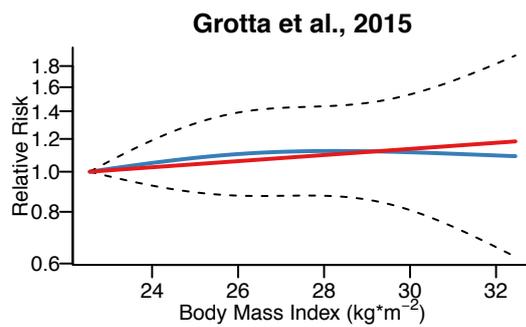
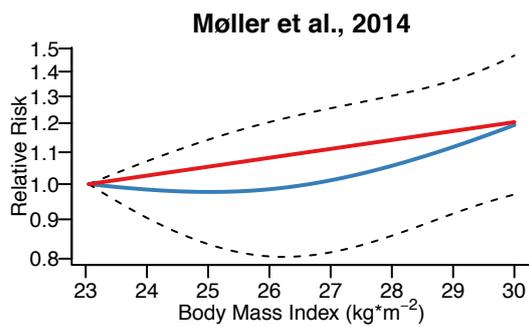
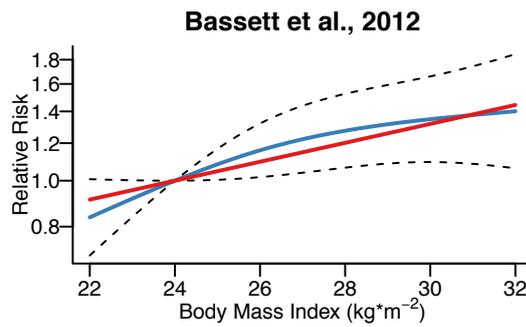
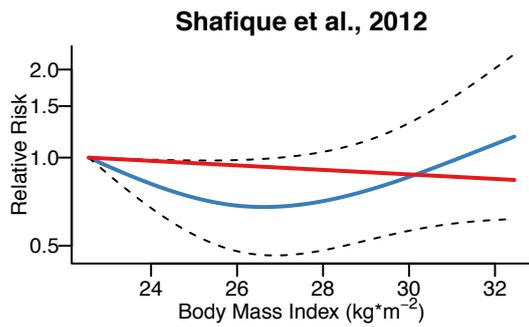
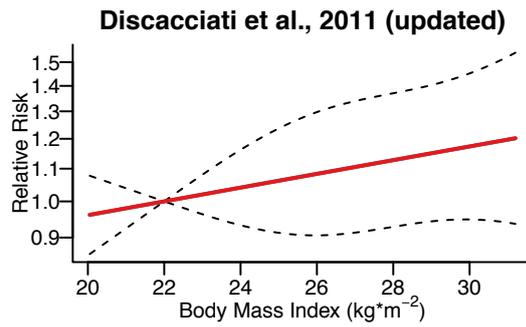
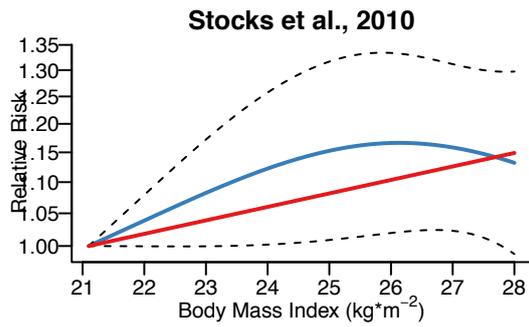
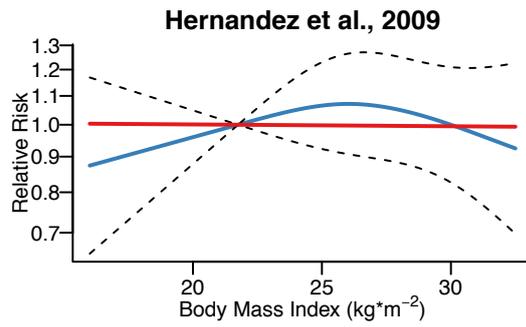
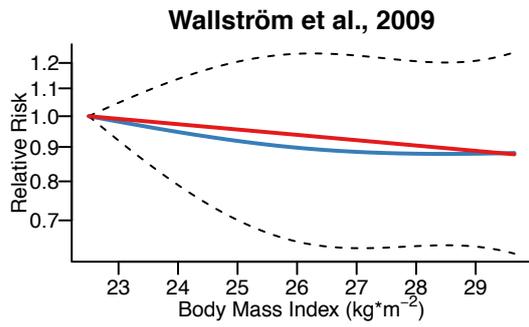


Figure A.4: Study-specific dose-response associations between BMI and incidence of advanced prostate cancer in the updated meta-analysis including 18 prospective studies. BMI was modeled using RCS with 3 knots positioned at the 10th, 50th, and 90th percentiles of the overall BMI distribution (blue line) and in a linear fashion (red line). Dashed black lines represent the 95% CI for the RCS models. The vertical axes are on the natural log scale. Figure continued on next page.



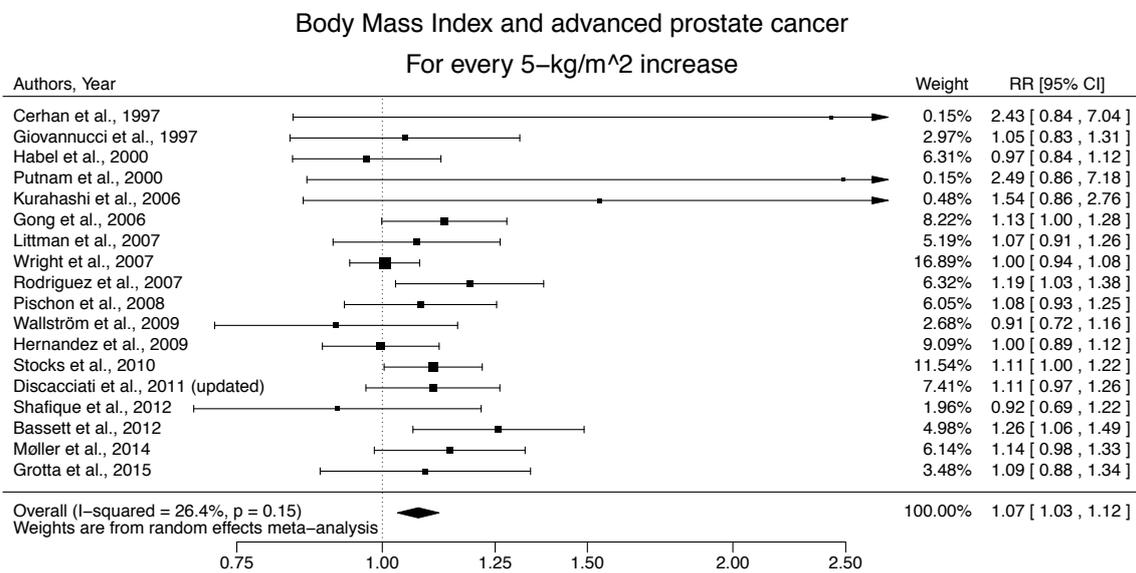


Figure A.5: RRs of advanced prostate cancer for every 5-unit increment in BMI for the updated dose-response meta-analysis on 18 prospective studies. The size of each square is proportional to the weight of the study (inverse of within- plus between-study variances)

Appendix B

Supplementary tables

Table B.1: Observed number of incident prostate cancer cases in the COSM by calendar year and attained age (top entry), and expected number of cases obtained by applying Swedish national rates to the COSM calendar-year and age structure (bottom entry).

Calendar year	Attained age (years)									Total
	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	
1998	1	1	8	26	36	48	49	4		173
	0	3	9	19	39	46	48	4		168
1999	0	5	16	28	39	61	64	10		223
	0	4	12	24	40	51	54	12		197
2000	0	6	16	33	40	43	65	23		226
	0	4	14	25	41	52	54	21		212
2001	0	5	16	32	59	47	61	36		256
	0	5	16	28	41	51	50	28		220
2002	0	4	23	27	46	51	69	38	0	258
	0	5	17	32	40	52	50	35	0	232
2003		6	26	53	63	79	72	59	5	363
		5	21	38	48	58	56	39	2	269
2004		7	15	50	57	74	72	47	7	329
		5	25	47	56	63	55	37	5	293
2005		4	28	47	77	60	76	51	13	356
		3	23	47	55	56	54	40	9	288
2006		2	22	34	58	49	49	40	21	275
		2	23	47	51	50	48	36	13	269
2007		0	21	57	57	58	36	51	29	309
		1	20	43	54	46	45	34	13	256
2008			19	52	75	39	49	35	34	303
			16	43	51	44	43	32	16	246
2009			15	70	72	49	59	47	31	343
			14	50	65	55	48	33	18	284
2010			9	52	57	59	54	30	20	281
			9	43	61	52	44	32	16	257
2011			7	41	63	61	39	45	19	275
			5	41	62	51	39	31	18	247
2012			5	28	63	48	46	32	21	243
			2	34	58	49	34	27	18	221
Total	1	40	246	630	862	826	860	548	200	4,213
	1	37	227	561	761	776	722	441	128	3,656

Table B.2: Observed number of prostate cancer deaths in the COSM by calendar year and attained age (top entry), and expected number of deaths obtained by applying Swedish national rates to the COSM calendar-year and age structure (bottom entry).

Calendar year	Attained age (years)									Total
	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	
1998	0	0	0	1	0	1	0	0		2
	0	0	1	2	6	12	18	2		43
1999	0	0	0	0	1	1	3	0		5
	0	0	1	2	6	12	19	7		47
2000	0	0	1	2	1	2	8	3		17
	0	0	1	3	6	12	20	12		53
2001	0	0	0	1	4	3	14	4		26
	0	0	1	3	6	11	19	16		56
2002	0	0	1	7	1	5	8	11	0	33
	0	0	1	2	4	11	17	20	0	56
2003		1	1	5	1	7	15	20	2	52
		0	1	3	5	13	21	23	3	69
2004		0	1	3	4	6	14	12	7	47
		0	1	2	7	11	18	23	8	70
2005		0	1	2	6	9	10	16	3	47
		0	1	3	6	11	18	23	11	73
2006		0	1	2	5	4	16	20	7	55
		0	1	3	5	9	17	24	17	77
2007		0	1	1	6	6	11	23	16	64
		0	1	3	5	9	18	23	21	79
2008			0	4	5	5	12	13	17	56
			1	3	5	8	16	24	26	82
2009			2	5	8	5	6	10	22	58
			1	2	5	9	15	22	28	81
2010			0	1	1	6	14	18	30	70
			0	2	5	8	15	22	30	82
2011			0	2	7	9	14	21	34	87
			0	2	6	8	13	21	32	82
2012			0	0	2	8	11	21	30	72
			0	2	5	8	12	22	34	84
Total	0	1	9	36	52	77	156	192	168	691
	0	2	12	37	82	152	255	284	209	1,034

Table B.3: Multivariable-adjusted IRRs of localized and advanced prostate cancer, and MRRs of fatal prostate cancer by categories of BMI at baseline age in the updated analysis of Paper I.

	BMI at baseline age, $\text{kg} \times \text{m}^{-2}$						For every 5-unit BMI increment
	<21.0	21.0–22.9	23.0–24.9	25.0–27.4	27.5–29.9	≥ 30.0	
Localized prostate cancer							
No. of cases/person-years	84/21,290	323/61,897	532/115,888	651/136,921	283/68,009	164/42,705	
IRR (95% CI)	0.77 (0.60–0.98)	1 (ref)	0.89 (0.77–1.02)	0.92 (0.79–1.06)	0.80 (0.67–0.95)	0.79 (0.64–0.98)	—
Advanced prostate cancer							
No. of cases/person-years	30/21,290	91/61,897	208/115,888	202/136,921	111/68,009	65/42,705	
IRR (95% CI)	0.89 (0.58–1.34)	1 (ref)	1.25 (0.98–1.61)	1.06 (0.82–1.37)	1.23 (0.91–1.65)	1.35 (0.95–1.92)	1.11 (0.96–1.27)
Fatal prostate cancer							
No. of cases/person-years	25/23,153	77/68,197	136/127,667	137/150,490	75/74,306	45/36,362	
MRR (95% CI)	0.85 (0.54–1.35)	1 (ref)	1.00 (0.76–1.33)	0.92 (0.69–1.23)	1.10 (0.78–1.54)	1.25 (0.83–1.89)	1.12 (0.95–1.32)

Table B.4: Multivariable-adjusted IRRs of localized and advanced prostate cancer, and MRRs of fatal prostate cancer by categories of BMI at age 30 years in the updated analysis of Paper I.

	BMI at age 30 years, $\text{kg}\times\text{m}^{-2}$						For every 5-unit BMI increment
	<21.0	21.0-22.9	23.0-24.9	25.0-27.4	27.5-29.9	≥ 30.0	
Localized prostate cancer							
No. of cases/person-years	391/81,774	714/144,676	631/139,388	220/59,843	61/13,895	20/7,133	
IRR (95% CI)	0.94 (0.82-1.07)	1 (ref)	0.97 (0.87-1.08)	0.88 (0.75-1.04)	1.14 (0.87-1.50)	0.77 (0.48-1.21)	1.00 (0.90-1.12)
Advanced prostate cancer							
No. of cases/person-years	133/81,774	247/144,676	220/139,388	86/59,843	14/13,895	7/7,133	
IRR (95% CI)	0.97 (0.58-1.34)	1 (ref)	0.93 (0.77-1.12)	0.96 (0.74-1.24)	0.74 (0.43-1.29)	0.75 (0.35-1.61)	0.92 (0.77-1.10)
Fatal prostate cancer							
No. of cases/person-years	103/89,861	172/159,460	153/152,789	50/65,330	11/15,145	6/7,691	
MRR (95% CI)	1.08 (0.84-1.39)	1 (ref)	0.94 (0.75-1.17)	0.82 (0.59-1.14)	0.86 (0.46-1.61)	0.98 (0.43-2.26)	0.84 (0.67-1.04)

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