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Anthropometric measures at multiple times throughout life and prostate cancer diagnosis, metastasis and death

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Abstract

Background: Previous studies of prostate cancer (PCa) risk and anthropometrics (i.e. body measurements) were based on single measurements or obtained over limited time spans.

Objective: To study the association between anthropometrics measured at multiple time-points in life and their relation to later diagnosis, metastasis or death from PCa.

Design, Setting, and Participants: This case-control study includes 27,167 Swedish men enrolled in two population-based projects during 1974 – 96. PCa diagnosis up to Dec. 31st 2006, disease information, gestation time, anthropometrics at birth, military conscript testing, and adulthood were collected. 1355 PCa-cases were matched with 5271 controls.

Outcome Measurements and Statistical Analysis: Univariate conditional logistic regression was used to determine whether clinical diagnosis, metastasis, or PCa death were associated with low birth weight (weight < 2500 g), Small for Gestational Age, or with weight, length or BMI at birth, adolescence (age 16-22), or early middle age (age 44-50).

Results and Limitation: Apart from weight at adolescence, which was associated with an increased risk of PCa diagnosis (OR per 5 kg (95%) 1.05 (1.01-1.09; P = 0.026)), pre-adulthood measurements were not associated with any PCa endpoint. Adulthood parameters were not associated with diagnosis. In contrast, weight and BMI at early middle age were significantly associated with metastasis (OR per 5 kg (95%) 1.13 (1.06-1.20; P<0.0001) and (OR (95%) 1.09 (1.05-1.14; P<0.0001) and death (OR per 5 kg (95%) 1.11 (1.03-1.19; P=0.005) and (OR (95%) 1.08 (1.03-1.13; P=0.003), respectively. It remains unclear whether these results apply to men of non-Caucasian origin, in populations with active PCa screening programs, or in countries without socialized health-care.

Conclusions: The analyses of these large data sets demonstrate significant effects of body characteristics (with links to metabolic syndrome) when measured at early middle age are associated with PCa disease severity, metastatic progression and outcome. Conversely, measurements at birth or adolescence are not associated with PCa prevalence or outcome,

Patient Summary: Increased weight and BMI in adults is associated with a higher risk of PCa metastasis and death.

Introduction and objectives

Understanding environmental factors that influence the risk of prostate cancer (PCa) could lead to strategies for its prevention. As PCa is the most commonly diagnosed cancer in men, even small shifts in incidence would have a large health and socioeconomic impact. PCa is particularly prevalent in Western countries suggesting that a Western lifestyle may influence risk, but the relative contribution of various aspects of diet, exercise and associated disease has not been definitively determined (1, 2). A considerable number of studies have examined the impact of metabolic disorders such as obesity, metabolic syndrome (MetS), diabetes mellitus type 2 (DMT2) on PCa risk. Most studies find that MetS is associated with an increased risk for a more aggressive PCa, whereas DMT2 is associated consistently with a lower risk (3-6). High body mass index (BMI) in adult life is associated with lower risks for PCa diagnosis in general, although overweight men tend to be diagnosed with more aggressive PCa compared to men of normal weight (7, 8).

The risk for developing MetS is a multifactorial process that begins at birth. Several studies have shown that low birth weight (LBW, <2500 g) and small for gestational age (SGA, birth weight <10th percentile compared to normal for the gestational age) predispose children to catch-up growth during the first years of life, increasing the later-in-life risk of obesity, DMT2, hypertension, hyperlipidemia and cardiovascular disease (9-16). Most recently, a Finnish study demonstrated a link between metabolic risk factors in children and adults (40). In addition, as was shown in a recent large scale, long-term follow-up study of Israeli men, adolescent BMI is a validated independent risk factor for chronic diseases later in life: risk for DMT2 and coronary heart disease increased by 9.8% and 12%, respectively, per increase in BMI unit at age 17) (17). The value of determining the association of early-in-life predictors of later metabolic disorders with cancer is well supported by prior literature (17-19).

With the aim to evaluate the correlation between MetS and PCa in more detail, and to devise evidence-based risk preventive programs, we determined if risk factors for MetS obtained for birth and up to middle age correlated with PCa risk. More specifically, we analyzed small for gestational age (SGA), low birth weight (LBW), adolescent and adult BMI (including height and weight as separate entities) with the risk of clinical PCa diagnosis, metastasis, and death. Our dataset incorporates an observational nested case control study design in a large representative cohort of Caucasian men with a median follow up from birth to 74 years. There is currently no active and ongoing PCa screening program in Sweden, and the data was obtained at a time when PSA was not widely used for detection of prostate cancer in the country. In general, the socialized health-care practices in Sweden provided the participants with equal care, unbiased by social status or income. Although several studies have investigated the correlation between PCa and anthropometrics related to MetS, no previous study has interrogated whether the effect is augmented during particular exposure windows in life. The correlation of PCa diagnosis with age made this a sensible question to ask.

Material and Methods

Study population

The study participants were males enrolled in the Malmö Preventive Project (MPP) and the Malmö Diet and Cancer study (MDCS). The MPP was a prospective preventive study begun in 1974, inviting all men born 1921-1949 living in Malmö to receive a baseline evaluation including a questionnaire, physical examination and blood sampling. In total 22,444 men enrolled, representing 74% of eligible participants (19). The MDCS was initiated as part of The European Prospective Investigation Into Diet and Cancer (EPIC) and began recruitment in 1991. The participants received a baseline evaluation including a questionnaire, physical examination and blood sampling. A total of 11,063 men, born

1923-45, were examined as part of the MDCS study, representing 41% of eligible men (29). A Personal Identity Number (PIN), unique for every Swedish citizen, was used for the purposes of tracking and merging of data from hospital charts, military conscript records, and national cancer registers (28).

Endpoint retrieval and matching of cases and controls

Our main endpoints were incident PCa, PCa metastasis and death due to PCa. By Dec 31st 2006, 1495 males in the MPP and 943 males in the MDCS were diagnosed with PCa according to the Swedish Cancer Registry. Because the two cohorts partially overlap, the total number of individuals with PCa is 1,851. A total of 48 PCa cases were excluded due to lack of information in medical records supporting a definitive diagnosis or due to diagnosis at autopsy. Furthermore, we excluded 448 cases for which no relevant weight information at either time point was available, leaving us with 1,355 unique cases. These cases were matched to 5271 controls who were alive and without a PCa-diagnosis at a date when the index case was diagnosed and who were born within a year of the index case. This left a total group of 5,726 men since some cases were also used as controls (Fig. 1). Using similar criteria – date of birth \pm 1 year, alive and free of the index event at the date of diagnosis of that event – we rematched on the outcome of PCa metastasis to obtain 237 cases and 945 controls; as well as on the outcome of PCa death, yielding 159 PCa death cases and 636 controls. Detection and determination of metastasis and death has been previously reported (30, 31).

Annotation and compilation of birth weight and length data

Anthropometry at birth for the study participants and last menstrual period of the mother were noted in the hospital chart of the mother. These data, stored in hospital and regional state archives under the hospital name and year, were located using the date of birth and parish of the study participants

and name and date of birth of the mother. The personal identity numbers (PIN) of the participants were sent to the Swedish Tax Agency and in return we received the name and date of birth of the mother and parish of the study participants. For persons born before 1930 we only received the parish of the study participants. Information for these men were then completed by searching for the name and date of the birth mother in parish records.

Anthropometry at birth (measured in grams and centimeters) was collected for participants born at hospitals in Skåne county of Sweden and major cities (Göteborg and Stockholm). Weight at birth was available for 3671 of the 5726 men. Birth weight data are missing on the study participants who were delivered at home by private midwives, had incomplete medical records, were immigrants or were born in hospitals other than the aforementioned.

Gestational time was calculated for each individual using the first date of the last menstrual period until birth date; for 658 individuals had the gestational time was approximated because last menstrual period was only noted as "beginning of", "middle of" or "end of" the month. Small for gestational age (SGA) was calculated using the weight percentiles calculator (32). SGA was defined as below the 10th percentile of the gestational age, and low birth weight (LBW) as birth weight below 2500 g.

Anthropometry at military conscript testing

Conscript testing for Military service in Sweden was mandatory until 2010, encompassing all male members of the cohorts. BMI data at conscript testing were retrieved from the Swedish National Military Archives, Stockholm. The charts were located using the specific military service number given to each individual. Ages at testing varied between 16 to 22 years, with a mean age of 19 years. BMI data were available for 5223 of the 5726 participants. Missing data was due to clearance of charts in

the Swedish National Military Archives and lack of data for non-Swedish born conscripts. Overweight was defined as BMI $>25 \text{ kg/m}^2$.

Anthropometry at adulthood

Weight and height were recorded as part of participation in the MDCS and MPP studies.

Documented evidence of PCa metastasis and cause of death

Incidences of metastasis were identified by reviewing medical charts from all included cases. We used a positive ^{99}Tc -MDP bone scan, CT, X-ray or MRI, or/and positive Pelvic Lymph Node Dissection (PLND) as criteria for metastatic burden. Imaging was performed as a staging tool, or as a result of increased blood biomarkers. Cause of death was obtained from the Cause of Death registry and confirmed by chart review that the actual cause of death was PCa.

Ethical considerations

This study was approved by the Ethical board of Lund University. DNR 2010/45 and 2007/268.

Statistical Analysis

Univariate conditional logistic regression was used to determine whether PCa diagnosis, metastasis or death from PCa were associated with continuous measures of birth length, weight, weight percentile given year of birth and gestational age, as well as length, weight, and body mass index (BMI) at military conscript testing and at adulthood. As a sensitivity analysis, we repeated our analyses dichotomizing birth weight ($< 2500 \text{ g}$ vs. $\geq 2500 \text{ g}$) i.e. low birth weight (LBW) and birth weight centile given birth year and gestation age (<10 centile vs. ≥ 10 centile) i.e. small for

gestational age (SGA). Because the relationship between anthropometry data and PCa may not be linear, we tested for non-linearity using restricted cubic splines with knots at the tertiles for the association between all predictors and all outcomes. We did not find evidence of non-linearity for any continuous predictor except in the relationship between PCa metastasis and BMI at adulthood.

We also tested whether diagnosis of PCa, PCa metastasis or death from PCa was related to the change in weight from birth to adolescence. Here, we repeated our analyses using proportionate weight change – weight change from birth to adolescence as a proportion of birth weight – and change in weight centile – from weight centile at birth given year of birth and gestational age to weight centile at military conscript testing given age at enrollment - as predictors in univariate conditional logistic regressions. Likewise, we repeated our analyses using percent change in height, weight or BMI from adolescence to adulthood as predictors of PCa diagnosis, PCa metastasis and death from PCa. Because of the case control design, absolute risks would be incorrect i.e. the average risk for PCa diagnosis, PCa metastasis and death from PCa would be at 25% due to the 3:1 matching. To correct for this, we calculated the true prevalence of each endpoint then used a statistical correction factor to adjust all calculated risks. Bootstrap resampling was used to estimate the 95% confidence intervals around those risks. Where significant nonlinearity was found, we also included cubic splines in these calculations.

All analyses were conducted using Stata 12.0 (Stata Corp., College Station, TX). A p-value less than 0.05 was considered significant.

Results

Participant characteristics are given in Table 1. There were 1355 men diagnosed with PCa before December 31st, 2006, with median age at diagnosis of 68 years. The mean time from study

enrollment to PCa diagnosis was 7 years in MDCS and 22 years in MPP. Our median follow up time from birth for men not diagnosed with prostate cancer was 74 years (IQR 69, 77).

Weight at adolescence was significantly associated with an increased risk of prostate cancer diagnosis ($p=0.026$), although the size of this effect is small. After correction for the case control design, the predicted risk of PCa diagnosis by weight at adolescence is shown in Figure 2. We did not find a significant association between adolescent weight and metastasis or death of disease, and the p value of 0.026 is unimpressive in the context of multiple testing.

In contrast to the lack of significant association between adolescence anthropometrics and prostate cancer outcomes, adulthood findings show that there is a relationship between weight and BMI and cancer aggressiveness. At adulthood we found there to be a significant association between anthropometrics and both the presence of PCa metastasis (both $p<0.0001$) as well as with PCa death ($p=0.005$ and $p=0.003$). The predicted risk of PCa metastasis and PCa death by weight and BMI at adulthood are shown in Figures 3-6, after correction for the case control design. Cubic splines were incorporated in the predicted risk of PCa metastasis by BMI at adulthood to account for the nonlinearity found in that relationship.

Our calculations further showed that the percentage change in weight and BMI from adolescence to adulthood was significantly associated with an increased risk of metastasis ($p=0.018$ and $p=0.015$) and PCa death ($p=0.030$ and $p=0.027$). However, these results are an artefact of the correlation between adult and adolescent BMI and weight. Change in BMI was not associated with outcome after controlling for adult BMI. Furthermore, our findings were similar when analysing for weight. No other individual parameters were found to have a statistically significant relationship with PCa endpoints.

Discussion

The aims of this study were to investigate whether risk factors relating to MetS are correlated to PCa risk, and to test if exposure to these factors are more distinct during a certain period of time in life. To answer these questions we designed a retrospective observational study based on a large, representative population-based cohort of men with low rates of PSA-testing and long-term follow up, for which PCa metastasis and cause of death had been carefully ascertained. Furthermore, this dataset included serial anthropometric measurements from birth to early middle age of a large cohort with a median follow up of 74 years from the earliest measurement. This data set has given us a unique opportunity to assess the PCa risk related to MetS risk factors throughout pre-adulthood (birth to adolescence) and adulthood (early middle age).

Our results show that, despite being strongly associated with future development of MetS, anthropometrics at birth and adolescence have no significant impact on future risk of prostate cancer. This work confirms published studies showing that increased BMI and weight in adulthood leads to an increased risk of aggressive and fatal PCa (7, 8, 41). Collectively, our findings suggest that obesity as an individual factor, rather than part of a metabolic syndrome, affects prostate cancer progression through yet undefined mechanisms. In the current study we did not find that men with high BMI had a decreased risk of PCa diagnosis, a finding at odds with the current literature. A possible explanation may be that our cohort was largely unscreened. The apparently protective effect of BMI on prostate cancer risk in screened men may be an artifact related to lower PSA levels in obese men. In addition to static measurements, we also analyzed if kinetic parameters were related to increased risk; surprisingly we did not notice any association with change in weight, height or BMI with diagnosis, metastasis or death from PCa.

Although prior studies have investigated the link between MetS factors and PCa, at least in part, we believe that the level of detail in our anthropometric data, the inclusion of multiple PCa outcome end-points, and the length of the follow-up contribute significant additional insight towards these important

questions. Previous studies investigating the impact of birth weight and PCa risk have been based on retrospective self-reported weight, or have failed to adjust weight for gestation time (20-27). Our study confirms prior findings failing to find an association between birth weight and risk of prostate cancer (24, 25). In a study based on a Danish cohort consisting of over 125 000 men, no significant association was found between prostate cancer risk and weights obtained from birth and up to pre-pubertal age. Although our data confirms this finding, the number of cases in this prior report was surprisingly low in relation to the cohort size, and disease related metastasis and death data were not included in their analysis (21). Further differences between the current work and previous studies are the corrected birth weights for gestational age; a parameter that has been shown to be an important risk factor for development of metabolic syndrome later in life. Although other studies have studied adolescent BMI or birth weight and risk for PCa (which reported no association), the inherent limited accuracy of retrospective self-reported anthropometric data is a considerable limitation (20, 23, 25, 27, 34).

Our study has several limitations. The cohort was almost exclusively Caucasian, and we do not know whether our conclusions would apply to men of other ethnic groups. We excluded birth weight data for participants who were delivered at home by private midwives (operating in rural areas) because of inexact, or incomplete, medical records. Until the mid 20th century, more than half of the births in rural areas were still delivered at home. It is of general notion that children from rural area who were delivered at home were healthier compared to children who had to be delivered at hospitals potentially creating a bias in our study. Moreover, our analysis necessarily adopted the shortcomings associated with the BMI calculation, and there is no opportunity to assess alternate weight criteria (*e.g.* abdominal obesity) within this cohort (26). Finally, compared to contemporary adult populations, there is an admittedly low prevalence of high BMI participants in our cohorts. Only 4% of the 5223 men with adolescent weight available had a BMI >25 kg/m². It should be considered these men are not fully developed adults, and the BMI range and distribution is normal for the age range (16).

However, such a low rate of overweight was not atypical for men in Sweden in the 1947-1969 (the era when the men in this study were aged 16-20). By 1988, 8% of the Swedish men aged 16-20 years were overweight or obese. In 2010 this number had risen to 16% (39). It should also be noted that, 44% of the men had a BMI over 25 kg/m² when the adult measurement was made. Although our results clearly point out that increased BMI and weight at early-middle age are associated with an increased risk for aggressive PCa disease, it is currently unclear if anthropometrics significantly adds to currently established risk prediction models. Further, we did not investigate if anthropometrics measured at different time-points in life were also associated with BPH (benign prostate hyperplasia) (42), which may potentially cause a detection bias.

Conclusions

This large observational study reinforces a growing body of data suggesting that anthropometrics at birth and adolescence, validated predictors for future risk of metabolic disorders, are not associated with PCa risk, metastasis or death. Our data further confirms that midlife or adult BMI and weight is associated with aggressive disease, but not to the diagnosis of PCa. We also note that the change over time of these parameters has no correlation to risk. Our findings suggest that further research is needed to better understand the mechanisms linking an unhealthy lifestyle and obesity with PCa aggressiveness and outcome.

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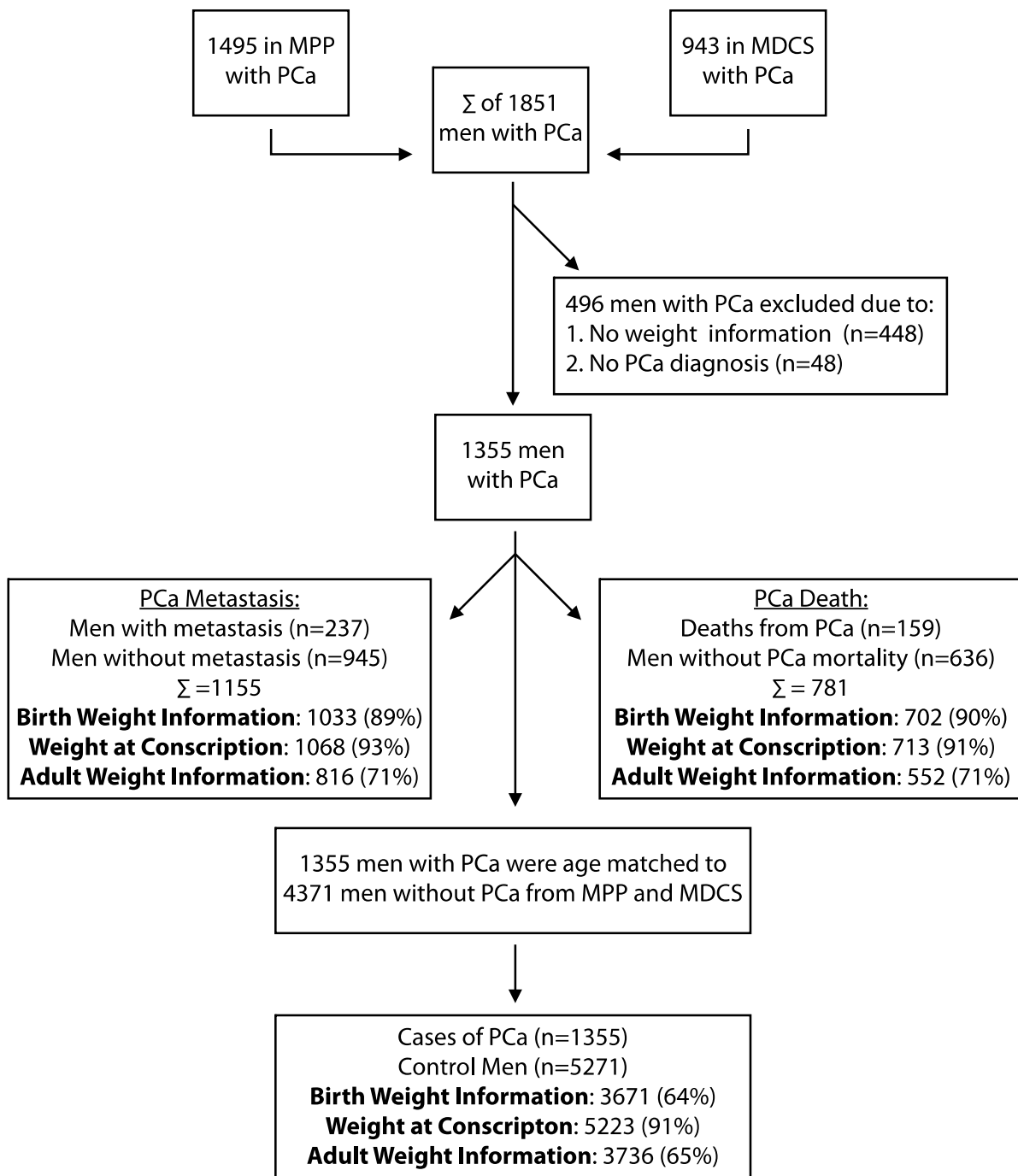


Fig 1. – Selection of cases and controls

Table 1. Patient characteristics. Data presented as medians with quartiles in parentheses or frequency with percentages in parentheses. Cases who were also used as controls are only represented in the cases group.

	Cases (N=1355; 24%)	Controls (N=4371; 76%)
Birth weight (g) (N=3671)	3600 (3220, 3918)	3550 (3200, 3890)
SGA (N=3632)	122 (15%)	406 (14%)
LBW (N=3671)	29 (3.5%)	91 (3.2%)
Weight at military enrollment (kg) (N=5223)	65 (61, 71)	65 (60, 70)
BMI at military enrollment (kg/m ²) (N=5223)	21 (20, 22)	21 (19, 22)
Weight at adulthood (kg) (N=5718)	78 (72, 86)	77 (71, 85)
BMI at adulthood (kg/m ²) (N=5718)	25 (23, 27)	24 (23, 27)

Figure 2. Predicted risk of prostate cancer diagnosis at 68 years of age by adolescent weight.

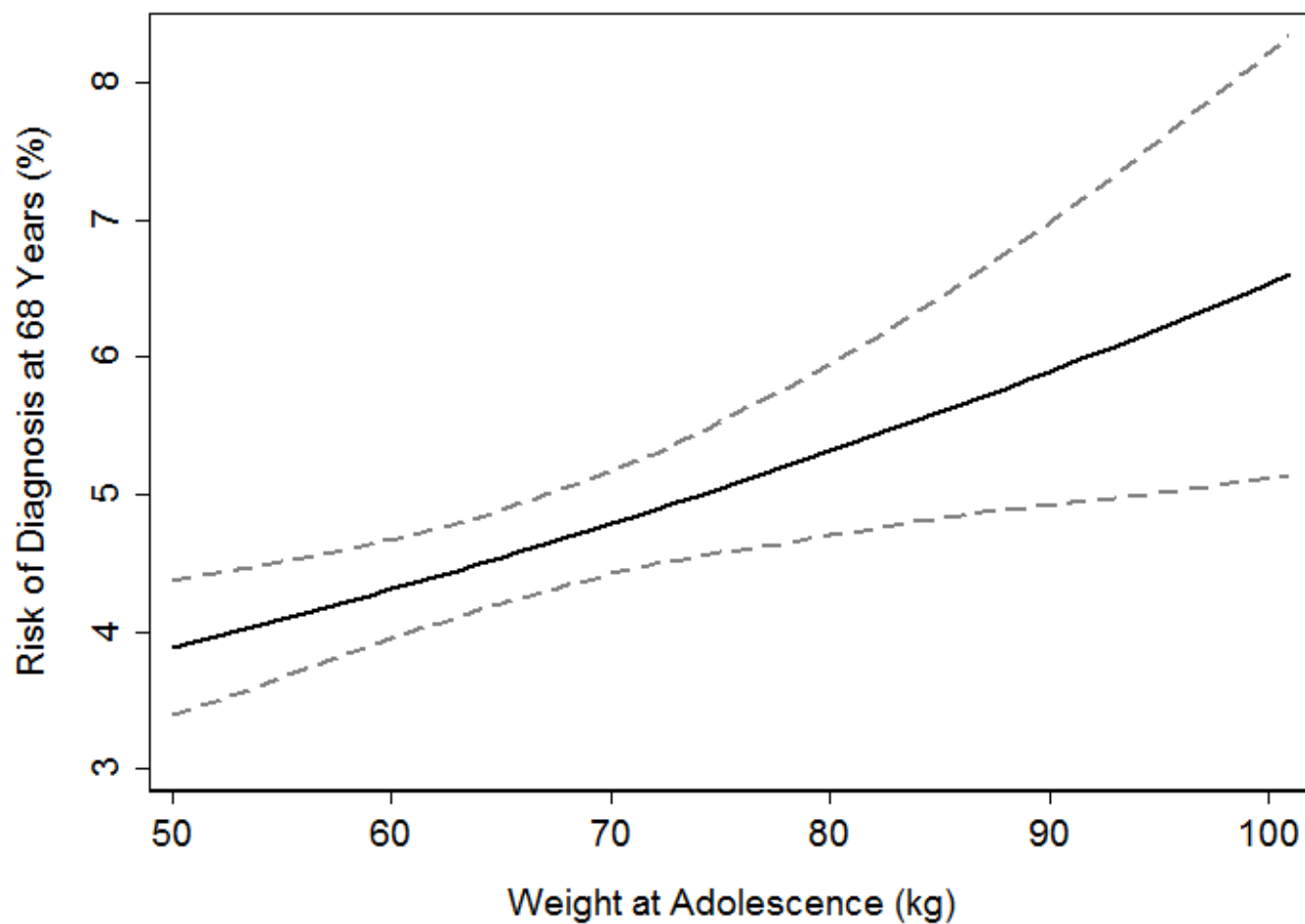


Figure 3. Predicted risk of prostate cancer metastasis at 70 years of age by adult weight.

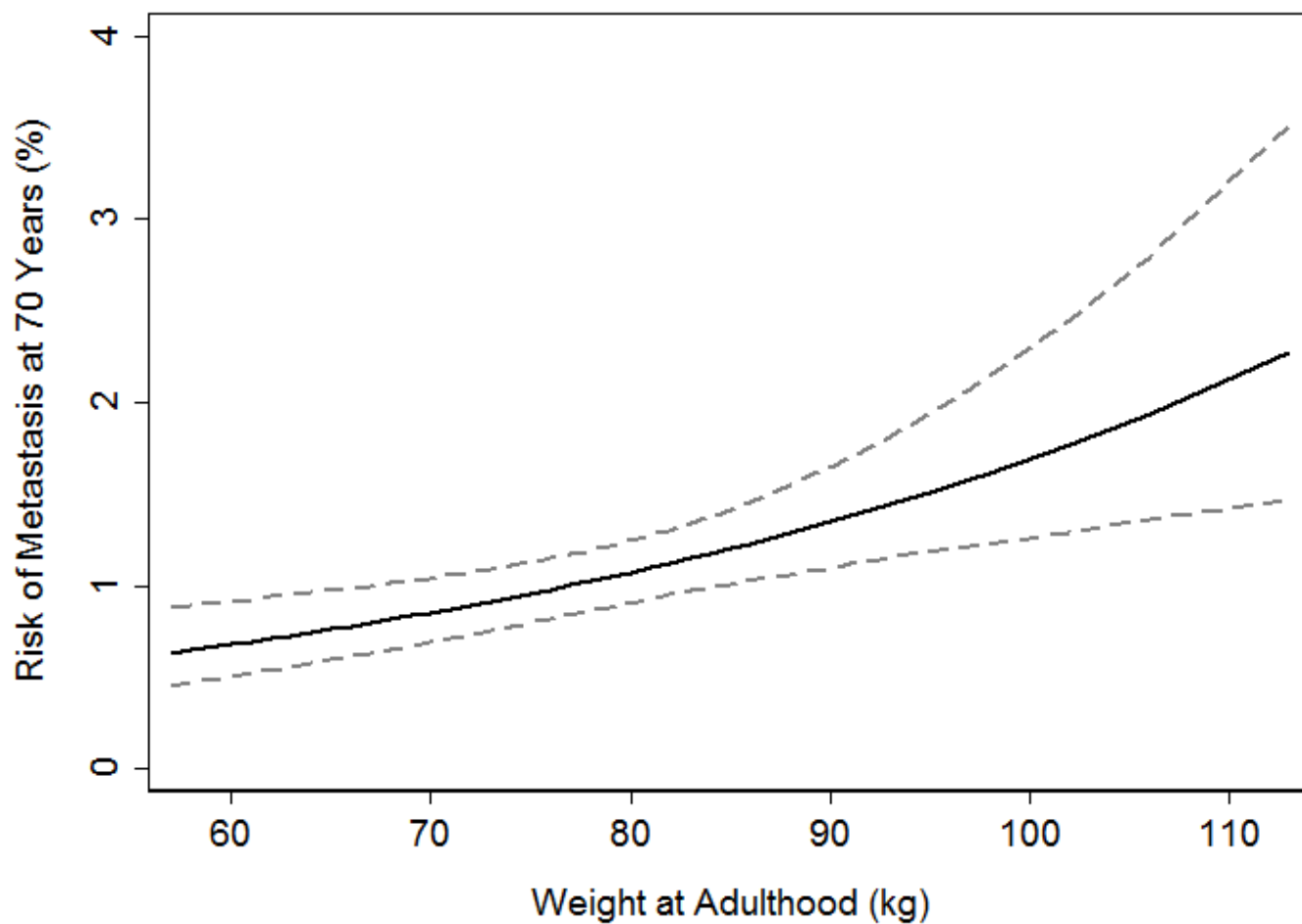


Figure 4. Predicted risk of prostate cancer metastasis at 70 years of age by adult BMI.

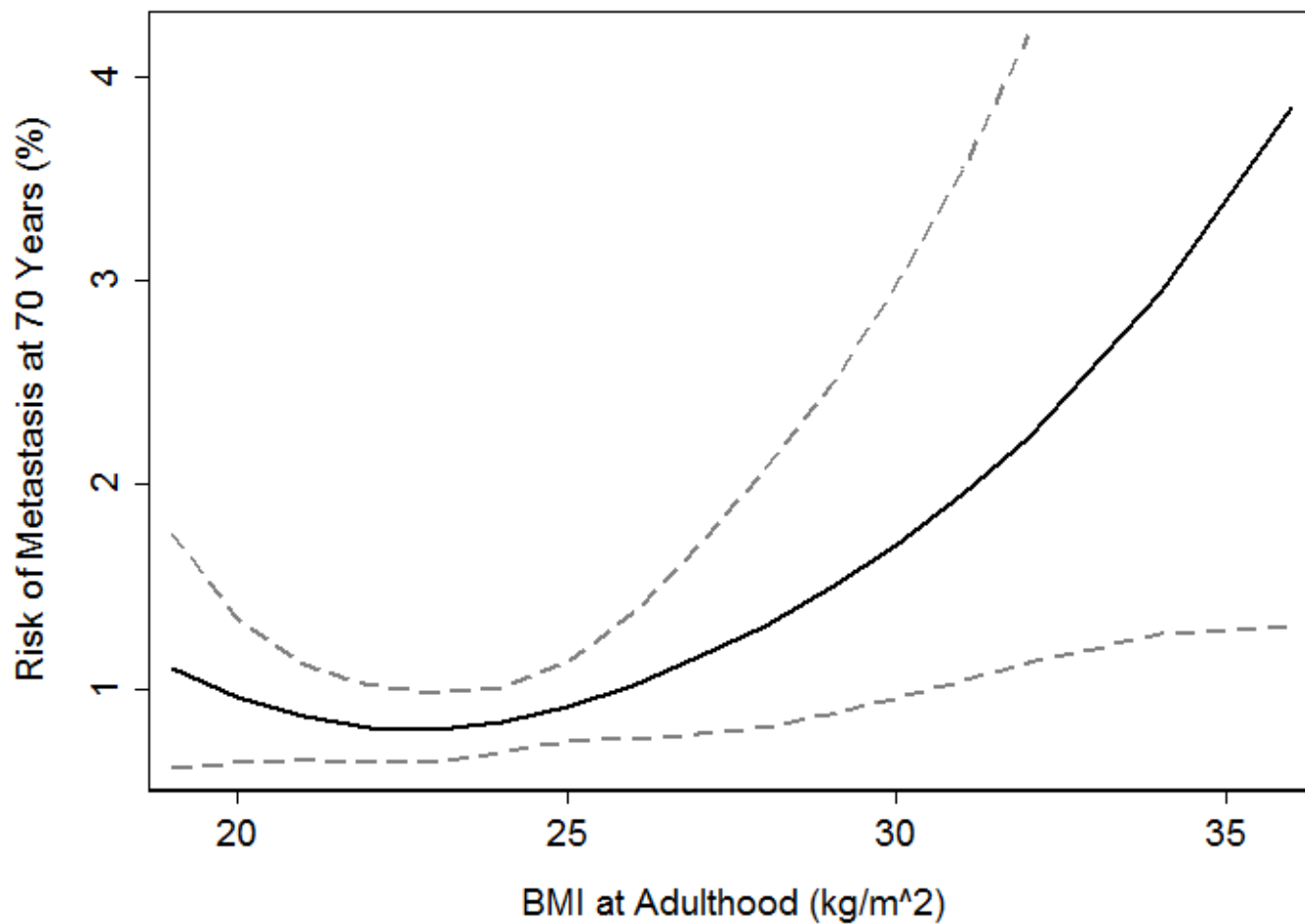


Figure 5. Predicted risk of death from prostate cancer at 71 years of age by adult weight.

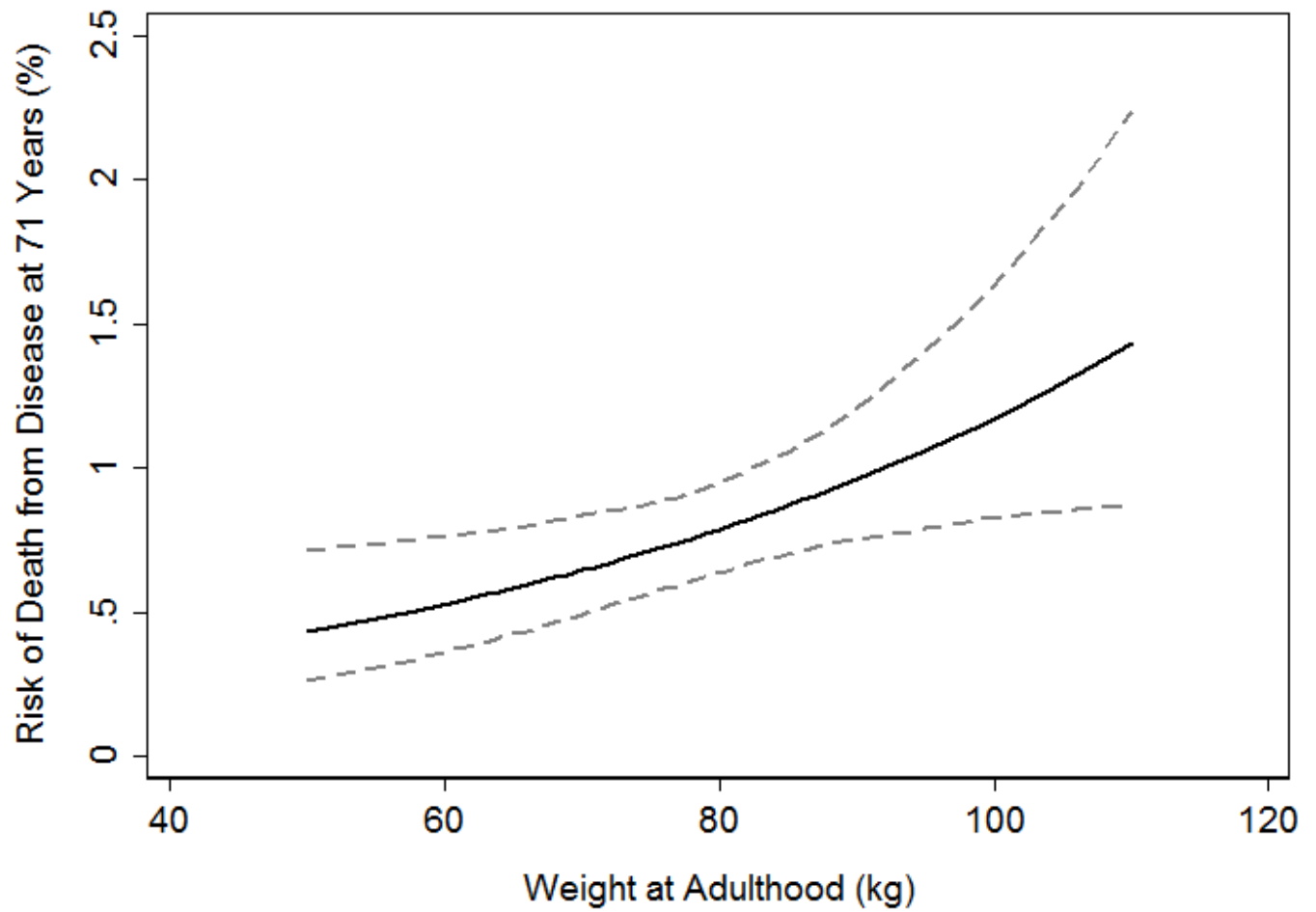


Figure 6. Predicted risk of death from prostate cancer at 71 years of age by adult BMI.

