Is birthweight associated with total and aggressive/lethal prostate cancer risks?  
A systematic review and meta-analysis

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Background: It has been hypothesised that intrauterine exposures are important for subsequent prostate cancer risk. Prior epidemiological studies have used birthweight as a proxy of cumulative intrauterine exposures to test this hypothesis, but results have been inconsistent partly because of limited statistical power.

Methods: We investigated birthweight in relation to prostate cancer in the Medical Research Council (MRC) National Survey of Health and Development (NSHD) using Cox proportional hazards models. We then conducted a meta-analysis of birthweight in relation to total and aggressive/lethal prostate cancer risks, combining results from the NSHD analysis with 13 additional studies on this relationship identified from a systematic search in four major scientific literature databases through January 2015.

Results: Random-effects models found that per kg increase in birthweight was positively associated with total (OR = 1.02, 95% confidence interval (95% CI) = 1.00, 1.05; \(I^2 = 13\%\)) and aggressive/lethal prostate cancer (OR = 1.08, 95% CI = 0.99, 1.19; \(I^2 = 40\%\)). Sensitivity analyses restricted to studies with birthweight extracted from medical records demonstrated stronger positive associations with total (OR = 1.11, 95% CI = 1.03, 1.19; \(I^2 = 0\%\)) and aggressive/lethal (OR = 1.37, 95% CI = 1.09, 1.74; \(I^2 = 0\%\)) prostate cancer. These studies heavily overlapped with those based in Nordic countries.

Conclusions: This study provides evidence that heavier birthweight may be associated with modest increased risks of total and aggressive/lethal prostate cancer, which supports the hypothesis that intrauterine exposures may be related to subsequent prostate cancer risks.

Prostate cancer is a significant public health burden and a major cause of morbidity and mortality among men worldwide. Few risk factors have been established for prostate cancer including advancing age, African ancestry, a family history of this malignancy and certain genetic polymorphisms (Al Olama et al, 2014). This may be partly owing to the fact that a majority of studies have focused on mid- to later-life exposures, and therefore may have missed putative aetiologically relevant time-windows, specifically early developmental stages of the prostate gland (Sutcliffe and Colditz, 2013). It has been hypothesised that intrauterine exposures may contribute to subsequent increased risk of prostate cancer (Ekholm, 1998), given that the hormonal and metabolic environment during pregnancy influences the physiological development of the prostate gland and may modulate hormonal sensitivity and prostate cancer risks in adult men (Ross and Henderson, 1994; Shibata and Minn, 2000). Although the biologic mechanisms underpinning a possible in utero origin of prostate cancer are not fully understood, intrauterine sex steroid...
hormones, insulin-like growth factors (IGFs) and elevated number of fetal stem cells (‘stem cell burden’ hypothesis; Ekborn, 1998) have been suggested to have important roles.

Direct epidemiological evidence linking intrauterine hormones and increased stem cell numbers to prostate cancer risk is sparse, likely because of the long latency period of tumour development and the challenge of accounting for changes in environmental factors after birth. Therefore, prior epidemiological studies have used birthweight as a proxy for cumulative intrauterine exposures for multiple chronic disease outcomes (Kuh and Ben-Shlomo, 2004). For example, birthweight has been extensively studied in relation to breast cancer and a recent meta-analysis suggested a positive dose–response relationship (dos Santos Silva et al, 2008). In relation to prostate cancer – another hormonally related malignancy – an early ecologic study demonstrated that mortality rates were positively correlated with country-level birthweight (Lawson, 1998). However, results to date from epidemiological studies of birthweight and prostate cancer risks have not consistently endorsed this relationship, partly because of insufficient statistical power, especially for aggressive/lethal prostate cancers, which are of greatest clinical relevance. Therefore, we performed a cohort analysis using the Medical Research Council (MRC) National Survey of Health and Development (NSHD), which extracted birthweight from medical records within a few weeks of delivery in 1946 and has subsequently accumulated nearly 70 years of follow-up. In addition, to provide a comprehensive assessment of birthweight in relation to total and aggressive/lethal prostate cancer risks, we conducted a systematic review and meta-analysis, combining results from our smaller NSHD analysis with those prior studies identified from systematic review.

MATERIALS AND METHODS

National Survey of Health and Development. We performed a cohort analysis in the NSHD birth cohort. A detailed description of this birth cohort has been published previously (Wadsworth et al, 2006). In brief, this cohort is a socially stratified and representative sample (N = 5362) of single live births in England, Scotland or Wales born in March 1946 and followed up ever since. Birthweight data were extracted from medical records within a few weeks of delivery. Characteristics of cohort members and their parents have been prospectively collected at follow-ups throughout life. Cohort members have been flagged on the National Health Service Central Register since 1971 (at the age of 25 years) for notification of cancer diagnoses, deaths and emigrations. We used Cox proportional hazards models with age as the underlying time scale to estimate hazard ratio (HRs) and 95% confidence intervals (CIs) of continuous (per kg) and categorical birthweight (< 3000, 3000–3499, 3500–3999 and ≥ 4000 g) in relation to total prostate cancer. Follow-up of this analysis started at the age of 25 years when cancer register data became available, and continued until prostate cancer diagnoses, deaths or emigrations. We used Cox proportional hazards models with age as the underlying time scale to estimate hazard ratio (HRs) and 95% confidence intervals (CIs) of continuous (per kg) and categorical birthweight (< 3000, 3000–3499, 3500–3999 and ≥ 4000 g) in relation to total prostate cancer.

Meta-analysis. For studies reporting results with categorical birthweight, we calculated individual unadjusted log odds ratios (ORs) per kg increase in birthweight and their standard errors using tabulated counts of cases and controls by birthweight category via methods described previously (Chene and Thompson, 1996). For studies reporting results with continuous birthweight, we back-calculated log risk estimates per kg and their standard errors using reported estimates and their 95% CIs. Unadjusted or minimally adjusted risk estimates were preferred over maximally adjusted estimates, given the fact that putative confounding factors showed little or no effect on estimates attained for the relationship between birthweight and prostate cancer risks in prior studies. This has the additional benefit of reducing excess heterogeneity attributable to different model specifications used in published studies. We pooled study-specific risk estimates using a random-effects meta-analytic model, and tested for between-study heterogeneity in risk estimates using a $I^2$ test based on the Q statistic, as well as the $I^2$ statistic and its 95% uncertainty interval (95% UI). To evaluate publication bias, we visually inspected the symmetry of funnel plots and quantitatively tested the bias using Begg’s rank correlation test and Egger’s linear regression test. To evaluate the influence of individual studies on the summary estimates, we performed influence analyses by leaving out one study at a time and re-estimating the summary estimates. We also performed meta-regression by separately including study-level covariates, such as birthweight source (medical records vs reported), country (Nordic vs non-Nordic), study population-based case–control (vs), mid-year birth (≤ 1945 vs > 1945; The World War II ends in 1945)), mean/median age at diagnosis (≤ 65 vs > 65 years) and adjustment status (no/minimal vs maximum), which were specified a priori. Finally, analyses were also conducted using fixed-effects models for the purpose of comparison and comprehensiveness. Meta-analyses were conducted separately for total and aggressive/lethal prostate cancers. All statistical analyses were performed using Stata version 13 (Stata Corp., College Station, TX, USA). Two-sided P-values < 0.05 were considered statistically significant.
RESULTS

NSHD results. Of the 2791 men in the NSHD birth cohort, 81 were diagnosed with prostate cancer through November 2014, of which 24 (30%) were diagnosed at ages younger than 60 years. Characteristics by event status are shown in Supplementary Table 1. Generally, these characteristics were evenly distributed by event status, except that fathers and maternal grandfathers of prostate cancer cases were more likely to have non-manual jobs, and mothers were more likely to have higher education compared with those of controls. Hazard ratios and 95% CIs estimated from Cox proportional hazards models are shown in Supplementary Table 2. In this NSHD analysis, neither continuous birthweight (OR\textsubscript{per kg increase} = 0.84, 95% CI = 0.56, 1.27) nor categorical birthweight (OR\textsubscript{<3000 g vs <3000 g} = 1.03, 95% CI = 0.54, 1.95; OR\textsubscript{3000–3499 g vs <3000 g} = 0.98, 95% CI = 0.51, 1.86; OR\textsubscript{3500–3999 g vs <3000 g} = 0.93, 95% CI = 0.42, 2.06) birthweight were significantly associated with prostate cancer. The proportional hazards assumptions held with nonsignificant Schoenfeld residuals test (P\textsubscript{continuous birthweight} = 0.103; P\textsubscript{categorical birthweight} = 0.478). As adjustment for father’s and maternal grandfather’s occupation as well as mother’s education did not materially change the results (Supplementary Table 2), we used unadjusted risk estimates in subsequent meta-analysis.

Literature search and study characteristics. A flow chart for this systematic review is shown in Figure 1. After independently screening titles, abstracts and key words, we deemed 49 articles to be potentially eligible and retrieved their full texts. After reviewing the full texts and their bibliographies, we included 14 studies in total (Ekbom et al, 1996, 2000; Boland et al, 2003; Kajantie et al, 2005; McCormack et al, 2005; Eriksson et al, 2007; Sutcliffe et al, 2007; Barker et al, 2012; Cook et al, 2013) including the NSHD analysis presented herein, 3 were nested case-control (Ekbom et al, 1996, 2000; Gerdtsson et al, 2015) and 3 were population-based case-control (Boland et al, 2003; Parent et al, 2008; Lope et al, 2012). Four of these 14 included studies used reported birthweight (Sutcliffe et al, 2007; Parent et al, 2008; Lope et al, 2012; Cook et al, 2013), 9 were conducted in Nordic countries (Ekbom et al, 1996, 2000; Kajantie et al, 2005; McCormack et al, 2005; Nilsen et al, 2005; Eriksson et al, 2007; Barker et al, 2012; Cook et al, 2013; Gerdtsson et al, 2015), and 8 reported the association between birthweight and aggressive/lethal prostate cancers (Ekbom et al, 1996; Kajantie et al, 2005; McCormack et al, 2005; Eriksson et al, 2007; Sutcliffe et al, 2007; Parent et al, 2008; Lope et al, 2012; Gerdtsson et al, 2015). Among those eight studies with subtype results, the Finnish study by Kajantie et al (2005) was the only study that did not report the association with total incident prostate cancer. Among excluded studies, five overlapped with the base populations of included studies (Tibblin et al, 1995; Platz et al, 1998; Ahlgren et al, 2007; Lahmann et al, 2010, 2012). Characteristics of included studies on birthweight in relation to prostate cancer risks are shown in Table 1.

Meta-analysis

Total prostate cancer. We pooled risk estimates from 13 studies for the risk of total prostate cancer per kg increase in birthweight using a random-effects model, and found that birthweight was associated with a small increased risk of the outcome (OR = 1.02, 95% CI = 1.00, 1.05; P = 0.045) (Figure 2). Publication bias was unlikely given the nonsignificant Begg’s (P = 0.583) and Egger’s

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Figure 1. Flow chart for systematic review.
| First author | Publication year | Study country | Study design | Birth weight source | Birth cohort | Year of recruitment/Dx | Sample size | Case number | Age at Dx | Control number | Exposure Measure | Adjustment for Covariates |
|--------------|------------------|---------------|--------------|-------------------|-------------|------------------------|------------|-------------|----------|---------------|-----------------|-------------------------|
| Lopea        | 2015             | Spain         | Population-based case-control | Self-reported at enrollment | ~1923–1973 | 2008–2015 | 15.37 | PCa (695); aggressive\textsuperscript{8} PCa (371) | ~6.0 (mean) | 324 | <2.5, 2.5–3.9, >3.9 kg | Matched by age at dx |
| Parent\textsuperscript{e} | 2015             | Canada, Montreal | Population-based case-control | Self-reported at enrollment | 1930–1968 | 2005–2009 | 32.78 | PCa (1621); aggressive\textsuperscript{8} PCa (440) | 65.0 (median) | 1657 | <5.5, 5.5–9.0, >9 lbs | Matched by age at dx |
| Boland       | 2003             | US, Minnesota | Population-based case-control | Minnesota birth certificate | 1941–1959 | 1988–1995 | 950 | PCa (192) | 51.1 (mean) | 3516 | Driver's license (374); Birth certificate listing (384) | Matched by birth year |
| Gerdtsson\textsuperscript{a} | 2015             | Sweden, Malmö | Nested case-control | Hospital chart | 1921–1949 | 1991–2006 | 4348 | PCa (832); metastasised PCa (237) | 68.0 (median) | 1880 | Per g; <3000, 3001–3500, 3501–4000, >4000 g | Matched by birth year and age at dx |
| Elborn       | 2000             | Sweden, Stockholm | Nested case-control | Standardised hospital chart | 1889–1941 | 1958–1994 | 2714 | PCa (834) | 61 (mean) | 691 | Per g | Matched by birth year and age at dx. Adjusted for maternal age, socioeconomic status, parity, pre-eclampsia/eclampsia and gestational age |
| Elborn       | 1996             | Sweden, Uppsala | Nested case-control | Standardised hospital maternity charts | 1874–1946 | 1958–1994 | 941 | PCa (250); PCa death (80) | 70.5 (mean) | 691 | Per g | Matched by birth year and age at dx. Adjusted for maternal age, socioeconomic status, parity, pre-eclampsia/eclampsia, prematurity, age at menarche and neonatal jaundice |
| Zhou\textsuperscript{g} | 2015             | UK             | Cohort | Birth record | 1946 | 1971–2014 | 2791 | PCa (81) | ~6.5 (median) | NA | Per kg; <3000, 3000–3499, 3500–3999, >4000 g | Matched by the birth year. Adjusted for age |
| Cook         | 2013             | Denmark, Copenhagen | Cohort | Reported by parent(s) at first school health examination | 1936–1969 | 1976–2010 | 93.625 | PCa (1699) | ~6.5 (mean) | NA | Per kg | Adjusted for birth year and age |
| Barke\textsuperscript{h} | 2012             | Finland        | Cohort | Birth records | 1934–1944 | 1971–2006 | 6975 | PCa (221); PCa death (5) | 61 (mean) | NA | Per kg | Unadjusted |
| Eriksson     | 2007             | Sweden, Gothenburg | Cohort | Obstetrics records | 1913 | 1963–1998 | 1436 | PCa (120); PCa death (68) | 74.2 (mean) | NA | Per g; <3000, 3001–4249, >4250 g | Adjusted for the birth year and age |
| Sutcliffe     | 2007             | US             | Cohort | Self-reported in 1994 | 1911–1946 | 1994–2002 | 20.266 | PCa (950); metastasised PCa (69) | 68 (mean) | NA | <5.5, 5.5–6.9, 7–8.4, 8.5–9.9, >10 lbs | Unadjusted |
Additional data from personal communications with Marie-Elise Parent from INRS-Institut Armand-Frappier, Canada.

dAggressive defined as Gleason score $\geq 7$ with primary pattern.

eAdditional data from personal communications with Dr David Ulmert from Memorial Sloan-Kettering Cancer Center, USA.

fMatching may be incomplete, given that men without birthweight information were excluded after matching and that the missing distributions may be different between cases and controls.

gThe analysis of MRC National Survey of Health and Development (NSHD) data, herein.

hAdditional data from personal communications with Drs Johan G Erikson from University of Helsinki, Finland and Clive Osmond from University of Southampton, UK.

iWe did not have information on tumour characteristics to evaluate the association with aggressive/lethal prostate cancer in this birth cohort, which may be because of the small number of events. Also, we did not have information on tumour characteristics to evaluate the association with aggressive/lethal prostate cancer in this birth cohort. However, our systematic review and meta-analysis suggests that greater birthweight is associated with small increased risks of total and aggressive/lethal prostate cancer. We detected a small amount of heterogeneity for total prostate cancer ($I^2 = 13\%$) but a moderate amount for aggressive/lethal disease ($I^2 = 40\%$). The associations of birthweight with total and aggressive/lethal prostate cancer risk. We found that per kg increase in birthweight seemed to be associated with an $8\%$ increased risk of aggressive/lethal disease (OR = 1.08, 95% CI = 0.99, 1.18; $P = 0.076$), although the association was not statistically significant (Figure 3). Publication bias was suggested by the asymmetry of the funnel plot (Supplementary Figure 2), yet objective judgment is difficult with only eight studies and Begg’s ($P = 0.266$) and Egger’s ($P = 0.054$) tests were not statistically significant. In influence analyses, the study by Parent et al (2008) was found to have an influence on the summary estimate, as the estimate became statistically significant and increased by 6% (OR = 1.14, 95% CI = 1.01, 1.28) once such study was removed (Supplementary Table 3). Of the eight studies included in this analysis, all Nordic studies had retrieved birthweight information from medical records, whereas all non-Nordic studies used reported birthweight. Subgroup analyses of the study-level variables showed that the moderate between-study heterogeneity ($I^2 = 40\%$, 95% UI = 0%, 73%; $P = 0.115$) may be explained by birthweight source/study country ($P = 0.020$) and study design ($P = 0.012$), with higher summary estimates for aggressive/lethal prostate cancer when restricted to Nordic studies that used medical record birthweight (OR per kg increase = 1.37, 95% CI = 1.09, 1.74), or studies in cohort/nested case–control designs (OR per kg increase = 1.14, 95% CI = 1.05, 1.24) (Table 2). For comparison and comprehensiveness, we performed fixed-effects meta-analysis, in which we found a slightly smaller but statistically significant overall summary result (OR per kg increase = 1.04, 95% CI = 1.00, 1.08; $P = 0.026$) as well as consistent subgroup results (Supplementary Table 4).

### DISCUSSION

We did not find a statistically significant association between birthweight and total prostate cancer risk in the NSHD birth cohort, which may be because of the small number of events. Also, we did not have information on tumour characteristics to evaluate the association with aggressive/lethal prostate cancer in this birth cohort. However, our systematic review and meta-analysis suggests that greater birthweight is associated with small increased risks of total and aggressive/lethal prostate cancer. We detected a small amount of heterogeneity for total prostate cancer ($I^2 = 13\%$) but a moderate amount for aggressive/lethal disease ($I^2 = 40\%$). The associations of birthweight with total and aggressive/lethal prostate cancer.
cancer were stronger when restricted to studies that used birthweight extracted from medical records or studies that were based in Nordic countries.

Although our meta-analysis estimated positive associations between birthweight and risks of total and aggressive/lethal prostate cancer, the magnitude of these associations was modest. However, we believe this modest magnitude is consistent with use of a proxy measure of the intrauterine environment rather than the possible causal exposure. Similar modest associations have also been observed for other results in utero markers and prostate cancer risk, consistent with our findings for birthweight. For example, shorter duration of gestation, which is associated with lower birthweight, has been inversely associated with prostate cancer risk (Ekbom et al, 1996), whereas higher parity (≥4) and placental weight, which are both associated with greater birthweight, have been positively associated with prostate cancer risk (Ekbom et al, 1996, 2000). In addition, taller adult height, another marker correlated with greater birthweight (Eide et al, 2005), was positively associated with total (ORper 5 cm = 1.04, 95% CI = 1.03, 1.05) and advanced (ORper 5 cm = 1.04, 95% CI = 1.02, 1.06) prostate cancer in a recent meta-analysis (World Cancer Research Fund International, 2014). Whether the link between birthweight and prostate cancer risks is mediated in full or part by adult height requires further investigation. Although birthweight is frequently used as a proxy of intrauterine exposures, the biologic height may be a possible birthweight–prostate cancer association that is not fully understood. Endogenous hormones, such as sex steroid hormones (Petridou et al, 1990; Peck et al, 2003) and IGFs (Orbak et al, 2001; Skalkidou et al, 2002; Davidson et al, 2006), and increased fetal stem cell burden (Strothsmitter et al, 2008; Capittini et al, 2011) in utero – all of which have demonstrated correlations with birthweight – have been hypothesised to modulate hormonal sensitivity and the risk of prostate cancer in adulthood.

Maternal and fetal sex steroid hormones act in concert in prenatal development, and homeostasis of both is essential for subsequent prostate health. The development of the prostate gland is androgen-dependent. Prostatic buds emerge from the urogenital sinus, which expresses androgen receptors stimulated by testicular androgens at approximately the tenth week of gestation (Cunha et al, 1987). It has been speculated that increased testosterone exposure in utero might reset the hypothalamic-pituitary-testicular feedback axis, leading to increased androgen secretion later in life. This hypothesis has been proposed to explain racial variation in prostate cancer risk (Ross and Henderson, 1994), as higher testosterone and oestradiol levels have been found in early gestational blood from African American than Caucasian women (Henderson et al, 1988; Potischman et al, 2005), higher testosterone to sex hormone-binding globulin concentration ratios have been found in cord blood from African American than their Caucasian counterparts in a recent meta-analysis (Richard et al, 2014). On the other hand, as fetal androgen levels decline and maternal oestrogen levels rise in the third trimester, exposure to excessive oestrogens may lead to squamous metaplasia in the fetus, although this pathological change regresses rapidly after birth when maternal oestrogens plummet (Ellem and Risbridger, 2009). Evidence for oestrogen carcinogenesis has been consistently documented in rodent studies, which have demonstrated that exposure to high-dose diethylstilbestrol and 17β-oestradiol during development can reprogramme the prostate gland and increase its susceptibility to carcinogenesis with ageing (Prins and Ho, 2010).

Other hormones regulating growth and metabolism may also have roles in subsequent prostate carcinogenesis. Insulin-like growth factors are required for prostate gland development (Ruan et al, 1999), and adult circulating concentrations have been positively associated with prostate cancer risk (Rowlands et al, 2009). Moreover, IGF-1 and IGFBP-3 concentrations in cord blood have been correlated with increased number of stem cell measures, which may confer higher susceptibility to later malignant transformation, and to a lesser extent, oestriol, oestriol and testosterone were also correlated with such (Baik et al, 2005).

![Figure 2. Birthweight (per kg) in relation to total prostate cancer risk by birthweight source using a random-effects model (N = 13).](image-url)
However, contrary to the expected direction of the association based on racial variation in prostate cancer risk, one study found that African-American neonates had lower concentrations of IGFs in cord blood than Caucasians (Rohrmann et al., 2009). Finally, leptin (Lai et al., 2011) and vitamin D (Eichholzer et al., 2013) cord blood levels were also similar in African-American and Caucasian neonates, suggesting that intrauterine exposure to these molecules is unlikely to explain racial differences in prostate cancer risk in adulthood.

This meta-analysis has several limitations that merit discussion. We cannot rule out measurement error in the three studies that used self-reported birthweight (Parent et al., 2008; Lope et al., 2012; Sutcliffe, 2007), given the fair-to-moderate agreement between self-reported and birth certificate-ascertained birthweight in prior validation studies (Jaworowicz et al., 2010); one cohort study that used maternal-reported birthweight (Cook et al., 2013) may have been subject to a lesser degree of measurement error (Adegboye and Heitmann, 2008). The stronger association observed in the subgroup of medical record-ascertained birthweight indirectly supports the possible existence of measurement error. Furthermore, we cannot exclude recall bias for two of these studies that ascertained birthweight information by self-report after prostate cancer diagnosis in a population-based case–control design (Parent et al., 2008; Lope et al., 2012), given that the summary estimate significantly increased by 10% (OR per kg increase = 1.14, 95% CI = 1.05, 1.24) for aggressive/lethal prostate cancer after omitting these two studies, although the summary estimate was not materially changed for total prostate cancer (OR per kg increase = 1.05, 95% CI = 1.01, 1.10; P = 0.024). Measurement error and recall bias usually attenuate associations, thus we may have underestimated the magnitude of the relationships between birthweight and prostate cancer risks. Second, we extracted/estimated unadjusted or minimally adjusted risk estimates from the majority of studies included, even though gestational age, maternal smoking, pregnancy-related and neonatal complications (e.g., pre-eclampsia/eclampsia and jaundice), birth order/parity and maternal anthropometric measures have been hypothesised to confound birthweight–prostate cancer associations. However, as prior studies to assess such factors found little or no effect on estimates (Boland et al., 2003; Nilsen et al., 2005; Eriksson et al., 2007; Zhou et al., herein), and as adjustment status was not significant in our subgroup analysis, we do not believe that use of minimally adjusted

### Table 2. Subgroup Analyses for birthweight (per kg) in relation to prostate cancer risks by random-effects models

| Subgroup                                | No. of studies | ORs  | 95% CIs       | P-value from meta-regression | I²  | 95% UIs | P-value |
|-----------------------------------------|---------------|------|---------------|-------------------------------|-----|---------|---------|
| **Total PCa**                           |               |      |               |                               |     |         |         |
| Source of birthweight                   |               |      |               |                               |     |         |         |
| Medical records                         | 9             | 1.11 | 1.03, 1.19    | 0.014                         |     | 0, 0.56 | 0.605   |
| Reported                                | 4             | 1.01 | 1.00, 1.03    |                               |     | 0, 0.68 | 0.700   |
| Study country                           |               |      |               |                               |     |         |         |
| Nordic                                  | 8             | 1.10 | 1.04, 1.16    | 0.005                         |     | 0, 0.47 | 0.746   |
| Other                                   | 5             | 1.01 | 0.99, 1.03    |                               |     | 0, 0.49 | 0.804   |
| Study design                            |               |      |               |                               |     |         |         |
| Cohort/nested case-control              | 10            | 1.06 | 1.01, 1.11    | 0.178                         |     | 0.94, 1.22 | 0.690   |
| Population-based case-control           | 3             | 1.01 | 0.98, 1.03    |                               |     | 0, 0.72 | 0.615   |
| Mid-birth cohort                        |               |      |               |                               |     |         |         |
| ≤1945                                   | 9             | 1.03 | 1.00, 1.06    | 0.913                         |     | 0.67, 1.24 | 0.182   |
| > 1945                                  | 4             | 1.03 | 0.95, 1.11    |                               |     | 0, 0.81 | 0.491   |
| Mean/median age at diagnosis            |               |      |               |                               |     |         |         |
| ≤65                                     | 6             | 1.01 | 0.99, 1.04    | 0.477                         |     | 0, 0.61 | 0.661   |
| > 65                                    | 7             | 1.06 | 0.99, 1.14    |                               |     | 0, 0.75 | 0.114   |
| Adjustment status                       |               |      |               |                               |     |         |         |
| No/minimal                             | 10            | 1.03 | 1.00, 1.06    | 0.648                         |     | 0, 0.66 | 0.173   |
| Maximum                                 | 3             | 1.05 | 0.97, 1.13    |                               |     | 0, 0.61 | 0.763   |
| **Aggressive/lethal PCa**               |               |      |               |                               |     |         |         |
| Source of birthweight                   |               |      |               |                               |     |         |         |
| Medical records                         | 5             | 1.37 | 1.09, 1.74    | 0.020                         |     | 0, 0.58 | 0.735   |
| Reported                                | 3             | 1.05 | 0.97, 1.13    |                               |     | 0, 0.86 | 0.129   |
| Study country                           |               |      |               |                               |     |         |         |
| Nordic                                  | 5             | 1.37 | 1.09, 1.74    | 0.020                         |     | 0, 0.58 | 0.735   |
| Other                                   | 3             | 1.05 | 0.97, 1.13    |                               |     | 0, 0.86 | 0.129   |
| Study design                            |               |      |               |                               |     |         |         |
| Cohort/nested case-control              | 6             | 1.14 | 1.05, 1.24    | 0.012                         |     | 0, 0.73 | 0.455   |
| Population-based case-control           | 2             | 1.02 | 0.98, 1.06    |                               |     | 0, NA   | 0.467   |
| Mid-birth cohort                        |               |      |               |                               |     |         |         |
| ≤1945                                   | 7             | 1.10 | 1.00, 1.22    | 0.265                         |     | 0, 0.77 | 0.095   |
| > 1945                                  | 1             | 0.92 | 0.70, 1.21    |                               |     | NA      | NA      |
| Mean/median age at diagnosis            |               |      |               |                               |     |         |         |
| ≤65                                     | 2             | 1.02 | 0.98, 1.06    | 0.291                         |     | 0, NA   | 0.609   |
| > 65                                    | 6             | 1.15 | 0.99, 1.33    |                               |     | 0, NA   | 0.235   |
| Adjustment status                       |               |      |               |                               |     |         |         |
| No/minimal                             | 7             | 1.08 | 0.99, 1.18    | 0.358                         |     | 0, 0.76 | 0.106   |
| Maximum                                 | 1             | 1.49 | 0.76, 2.91    |                               |     | NA      | NA      |

Abbreviations: CI = confidence interval; NA = not applicable; OR = odds ratio; PCa = prostate cancer; UI = uncertainty interval.
estimates influenced our conclusions (Table 1). Third, longitudinal anthropometric measures, such as adult height, were only ascertained in two of the included studies (Cook et al, 2013; Gerdsson et al, 2015). As these studies observed different results for anthropometric measures, we are unable to evaluate to what extent the effects of birthweight may be mediated by adult height. Fourth, we cannot exclude the possibility of publication bias for the meta-analysis on aggressive/lethal prostate cancer, given that only eight studies presented results for this subgroup of cases. Last, studies included in this meta-analysis were primarily conducted in men with European ancestry, and therefore we were unable to evaluate whether birthweight is associated with prostate cancer risks in men with African ancestry.

In conclusion, this systematic review and meta-analysis suggests that heavier birthweight may be associated with modest increased risks of total and aggressive/lethal prostate cancer. Novel approaches and longitudinal data are needed in future birth cohorts to elucidate biological mechanisms and determine the aetiological time windows for prostate carcinogenesis.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Figure 3. Birthweight (per kg) in relation to aggressive/lethal prostate cancer risk by birthweight source using a random-effects model (N = 8).

| Study Year | Study country | Medical records | Kajantie 2005 Finland | Nilsen 2005 Norway | Eriksson 2007 Sweden, Gothenburg | Gerdsson 2015 Sweden, Malmo | Subtotal (I² = 0.0%, P = 0.735) |
|------------|---------------|-----------------|----------------------|-----------------|-----------------------------|---------------------------|-------------------------------|
| Elkbom 1996 Sweden, Uppsala | 1.49 (0.76, 2.91) | 2.38 (0.98, 5.80) | 1.24 (0.58, 2.64) | 1.41 (0.93, 2.13) | 1.22 (0.83, 1.78) | 1.37 (1.09, 1.74) |
| Subtotal | 1.08 (0.99, 1.18) | 100.00 |

The authors declare no conflict of interest.

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