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Keywords: birthweight; prostatic neoplasms; meta-analysis; review

# 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 (Ekbom, 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

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hormones, insulin-like growth factors (IGFs) and elevated number of fetal stem cells ('stem cell burden' hypothesis; Ekblom, 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  $\geq 4000$  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 diagnosis, death, emigration or age 67 years (i.e., until November 2014, the most recent date of available cancer registry data), whichever occurred earlier. We included 2791 men in this analysis, after excluding 2547 females, 17 men without birthweight information and 7 without follow-up information.

**Literature search.** To complement the NSHD analysis and increase the statistical power, we also conducted a systematic review on the relationship between birthweight and prostate cancer risks. Four major scientific literature databases (PubMed (National Centre for Biotechnology Information, US National Library of Medicine, Bethesda, MD, USA), EMBASE (Elsevier BV, Amsterdam, The Netherlands), Scopus (Elsevier BV), Web of Science (Thomson Reuters, New York, NY, USA)) were systematically searched through January 2015 by a trained clinical informationist (JW).

No date or language restrictions were applied. Search terms incorporated a wide array of variables for, or related to, birthweight and prostate cancer or cancer in general. Search strategies are available from the authors on request. Two reviewers (CKZ and MBC) independently assessed titles, abstracts and keywords to select potentially relevant studies from retrieved references. Discordant selections were resolved by consensus. The full text of any original contribution that indicated a potential to contain data on birthweight and prostate cancer, or of any review on prostate cancer aetiology, was retrieved. Bibliographies of retrieved full-text articles were also reviewed to identify references that may have been missed or absent from the databases used. We contacted corresponding authors for additional data if their publications did not present adequate information necessary for meta-analysis. References were compiled and managed using Endnote X7. To be included in this meta-analysis, a published study had to fulfill the following criteria: (1) study populations were born as singletons; (2) have at least 20 cases and 20 controls in the analysis; (3) used a cohort or case–control study design; and (4) provided risk estimates with 95% CIs per unit change in birthweight, or tabulated counts of cases and controls by birthweight category to allow for log-linear coefficients and standard errors to be estimated using methods described previously (Chene and Thompson, 1996). When multiple reports were published with substantial geotemporal overlap in the base population, we included the most recent or best-powered publication. Two reviewers (CKZ and MBC) independently extracted data from selected articles according to a standard form created *a priori* for this study. Differences were resolved by consensus.

**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  $\chi^2$  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), design (cohort/nested case–control *vs* population-based case–control), mid-birth year ( $\leq 1945$  *vs*  $> 1945$ ; The World War II ends in 1945), mean/median age at diagnosis ( $\leq 65$  *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 ( $OR_{\text{per kg increase}} = 0.84$ , 95% CI = 0.56, 1.27) nor categorical ( $OR_{3000-3499 \text{ vs } < 3000 \text{ g}} = 1.03$ , 95% CI = 0.54, 1.95;  $OR_{3500-3999 \text{ vs } < 3000 \text{ g}} = 0.98$ , 95% CI = 0.51, 1.86;  $OR_{\geq 4000 \text{ vs } < 3000 \text{ g}} = 0.93$ , 95% CI = 0.42, 2.06) birthweight were significantly associated with prostate cancer. The proportional hazards assumptions held with nonsignificant Schoenfeld residuals test ( $P_{\text{continuous birthweight}} = 0.103$ ;  $P_{\text{categorical birthweight}} = 0.478$ ). 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; Nilsen *et al*, 2005; Eriksson *et al*, 2007; Sutcliffe *et al*, 2007; Parent *et al*, 2008; Barker *et al*, 2012;

Lope *et al*, 2012; Cook *et al*, 2013; Gerdtsson *et al*, 2015) including the NSHD analysis presented herein for qualitative and quantitative synthesis, 8 of which were cohort in design (Kajantie *et al*, 2005; McCormack *et al*, 2005; Nilsen *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; Nilsen *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

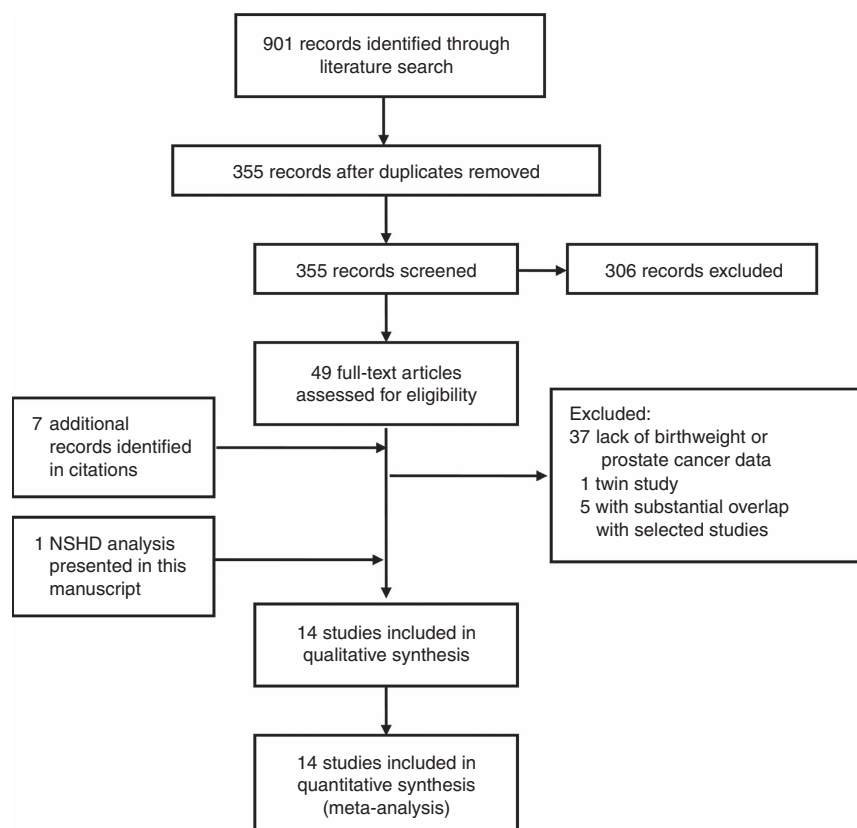


Figure 1. Flow chart for systematic review.

**Table 1. Characteristics of included studies on birthweight in relation to prostate cancer risks (N = 14)**

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
Lope <sup>a</sup>	2015	Spain	Population-based case-control	Self-reported at enrollment	~1923-1973	2008-2015	1537	PCa (695); aggressive <sup>b</sup> PCa (371)	~66.0 (mean)	324	<2.5, 2.5-3.9, >3.9 kg	Matched by age at dx
Parent <sup>c</sup>	2015	Canada, Montreal	Population-based case-control	Self-reported at enrollment	1930-1968	2005-2009	3278	PCa (1621); aggressive <sup>d</sup> 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)	Driver's license (374); Birth certificate listing (384)	≤3000, 3001-3500, 3501-4000, >4000 g	Matched by birth year
Gerdts <sup>son</sup> <sup>e</sup>	2015	Sweden, Malmö	Nested case-control	Hospital chart	1921-1949	1991-2006	4348	PCa (832); metastasised PCa (237);	68.0 (median)	3516	Per g: ≤3000, 3001-3500, 3501-4000, >4000 g	Matched by birth year and age at dx <sup>f</sup>
Ekbom	2000	Sweden, Stockholm	Nested case-control	Standardised hospital chart	1889-1941	1958-1994	2714	PCa (834)		1880	Per g	Matched by birth year and age at dx. Adjusted for maternal age, socioeconomic status, parity, pre-eclampsia/eclampsia and gestational age
Ekbom	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 <sup>g</sup>	2015	UK	Cohort	Birth record	1946	1971-2014	2791	PCa (81)	~60.5 (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	93625	PCa (1699)	~65 (mean)	NA	Per kg	Adjusted for birth year and age
Barker <sup>h</sup>	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	Pper g: ≤3000, 3001-4249, ≥4250 g	Adjusted for the birth year and age
Surcliffe	2007	US	Cohort	Self-reported in 1994	1911-1946	1994-2002	20266	PCa (950); metastasised PCa (69)	68 (mean)	NA	<5.5, 5.5-6.9, 7-8.4, 8.5-9.9, ≥10 lbs	Unadjusted <sup>i</sup>

**Table 1. (Continued)**

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
Kajantie	2005	Finland	Cohort	Birth record	1924–1944	1971–1998	7203	PCa death (22)	65.2 <sup>l</sup> (mean)	NA	Per kg	Adjusted for birth years and gestational age
McCormack	2005	Sweden, Uppsala	Cohort	Obstetric notes	1915–1929	1960–2001	5820	PCa (405)	68.4 <sup>k</sup> (median)	NA	Per kg	Adjusted for age and gestational age
Nilsen	2005	Norway	Cohort	Birth records	1920–1958	1961–2001	19 681	PCa (159); metastasised PCa (33)	65.0 (median)	NA	<3260, 3260–3590, 3595–3920, ≥3925 g	Unadjusted

Abbreviations: dx = diagnosis; g = gram; kg = kilogram; MRC = Medical Research Council; PCa = prostate cancer; NA = not applicable; NSHD = National Survey of Health and Development; s.d. = standard deviation; UK = United Kingdom; USA = United States of America. The table is sorted by study design and reverse chronological order of publication year.

<sup>a</sup>Additional data from personal communications with Dr Virginia Lope from Carlos III Institute of Health, Spain.

<sup>b</sup>Aggressive defined as Gleason score ≥ 7.

<sup>c</sup>Additional data from personal communications with Marie-Elise Parent from INRS-Institut Armand-Frappier, Canada.

<sup>d</sup>Aggressive defined as Gleason score ≥ 7 with primary pattern = 4.

<sup>e</sup>Additional data from personal communications with Dr David Ulmer from Memorial Sloan-Kettering Cancer Center, USA.

<sup>f</sup>Matching may be incomplete, given that men without birth weight information were excluded after matching and that the missing distributions may be different between cases and controls.

<sup>g</sup>The analysis of MRC National Survey of Health and Development (NSHD) data, herein.

<sup>h</sup>Additional data from personal communications with Dris Johan G Erikson from University of Helsinki, Finland and Clive Osmond from University of Southampton, UK.

<sup>i</sup>Results presented in the abstract were age-adjusted.

<sup>j</sup>Age at prostate cancer death.

<sup>k</sup>Age at diagnosis of all male cancers.

( $P=0.202$ ) tests, although the funnel plot appeared slightly asymmetric (Supplementary Figure 1). Omission of one study at a time did not materially change the summary risk estimate (Supplementary Table 3). In particular, when Sutcliffe *et al* (2007) or Parent *et al* (2008) – which had the greatest weights – were excluded, the summary risk estimates did not deviate from the overall risk estimate. Subgroup analyses of study-level variables showed that birthweight source ( $P=0.014$ ) and country ( $P=0.005$ ) may partially explain the small amount of between-study heterogeneity detected, with higher summary risk estimates for studies that used medical records to ascertain birthweight ( $OR_{\text{per kg increase}} = 1.11$ , 95% CI = 1.03, 1.19) and studies in Nordic countries ( $OR_{\text{per kg increase}} = 1.10$ , 95% CI = 1.04, 1.16) (Table 2). Seven of the nine studies that used medical records to ascertain birthweight were based in Nordic countries. Given the heterogeneity test was not statistically significant ( $P=0.312$ ) with  $I^2 = 13\%$  (95% UI = 0%, 52%), we performed sensitivity analyses using fixed-effects models, which provided similar overall ( $OR_{\text{per kg increase}} = 1.02$ , 95% CI = 1.00, 1.03;  $P=0.028$ ) and subgroup summary estimates (Supplementary Table 4).

**Aggressive/lethal prostate cancer.** We separately conducted a meta-analysis using a random-effects model of eight studies that provided birthweight in relation to 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 ( $OR_{\text{per kg increase}} = 1.37$ , 95% CI = 1.09, 1.74), or studies in cohort/nested case-control designs ( $OR_{\text{per kg increase}} = 1.14$ , 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 ( $OR_{\text{per kg increase}} = 1.04$ , 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

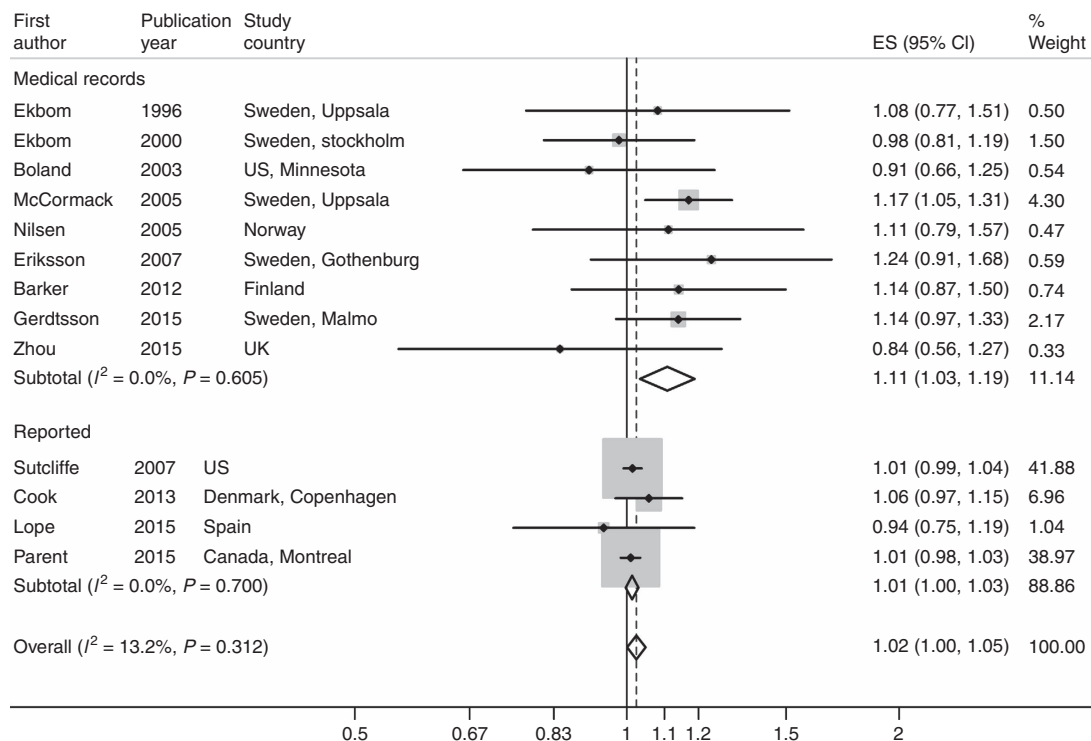


Figure 2. Birthweight (per kg) in relation to total prostate cancer risk by birthweight source using a random-effects model ( $N = 13$ ).

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 *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 ( $\geq 4$ ) 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 ( $OR_{per\ 5\ cm} = 1.04$ , 95% CI = 1.03, 1.05) and advanced ( $OR_{per\ 5\ cm} = 1.04$ , 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 mechanisms underlying a possible birthweight–prostate cancer association are 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 (Strohsnitter *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 male neonates (Rohrmann *et al*, 2009), and higher age-adjusted free testosterone concentrations were found in healthy adult African American men 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 can induce aberrant proliferation of the prostatic epithelium, which 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 17  $\beta$ -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, oestradiol, oestriol and testosterone were also correlated with such (Baik *et al*, 2005).



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

	No. of studies	ORs	95% CIs	P-value from meta-regression	Heterogeneity		
					I <sup>2</sup>	95% UIs	P-value
<b>Total PCa</b>							
<b>Source of birthweight</b>				0.014			
Medical records	9	1.11	1.03, 1.19		0	0, 56	0.605
Reported	4	1.01	1.00, 1.03		0	0, 68	0.700
<b>Study country</b>				0.005			
Nordic	8	1.10	1.04, 1.16		0	0, 47	0.746
Other	5	1.01	0.99, 1.03		0	0, 49	0.804
<b>Study design</b>				0.178			
Cohort/nested case-control	10	1.06	1.01, 1.11		25	0, 64	0.216
Population-based case-control	3	1.01	0.98, 1.03		0	0, 72	0.690
<b>Mid-birth cohort</b>				0.913			
≤ 1945	9	1.03	1.00, 1.06		30	0, 67	0.182
> 1945	4	1.03	0.95, 1.11		0	0, 81	0.491
<b>Mean/median age at diagnosis</b>				0.477			
≤ 65	6	1.01	0.99, 1.04		0	0, 61	0.661
> 65	7	1.06	0.99, 1.14		42	0, 75	0.114
<b>Adjustment status</b>				0.648			
No/minimal	10	1.03	1.00, 1.06		30	0, 66	0.173
Maximum	3	1.05	0.97, 1.13		0	0, 61	0.763
<b>Aggressive/lethal PCa</b>							
<b>Source of birthweight</b>				0.020			
Medical records	5	1.37	1.09, 1.74		0	0, 58	0.735
Reported	3	1.05	0.97, 1.13		51	0, 86	0.129
<b>Study country</b>				0.020			
Nordic	5	1.37	1.09, 1.74		0	0, 58	0.735
Other	3	1.05	0.97, 1.13		51	0, 86	0.129
<b>Study design</b>				0.012			
Cohort/nested case-control	6	1.14	1.05, 1.24		0	0, 73	0.455
Population-based case-control	2	1.02	0.98, 1.06		0	NA	0.467
<b>Mid-birth cohort</b>				0.265			
≤ 1945	7	1.10	1.00, 1.22		44	0, 77	0.095
> 1945	1	0.92	0.70, 1.21		NA	NA	NA
<b>Mean/median age at diagnosis</b>				0.291			
≤ 65	2	1.02	0.98, 1.06		0	NA	0.609
> 65	6	1.15	0.99, 1.33		27	0, 69	0.235
<b>Adjustment status</b>				0.358			
No/minimal	7	1.08	0.99, 1.18		43	0, 76	0.106
Maximum	1	1.49	0.76, 2.91		NA	NA	NA

Abbreviations: CI = confidence interval; NA = not applicable; OR = odds ratio; PCa = prostate cancer; UI = uncertainty interval.

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<sub>per kg increase</sub> = 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<sub>per kg increase</sub> = 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

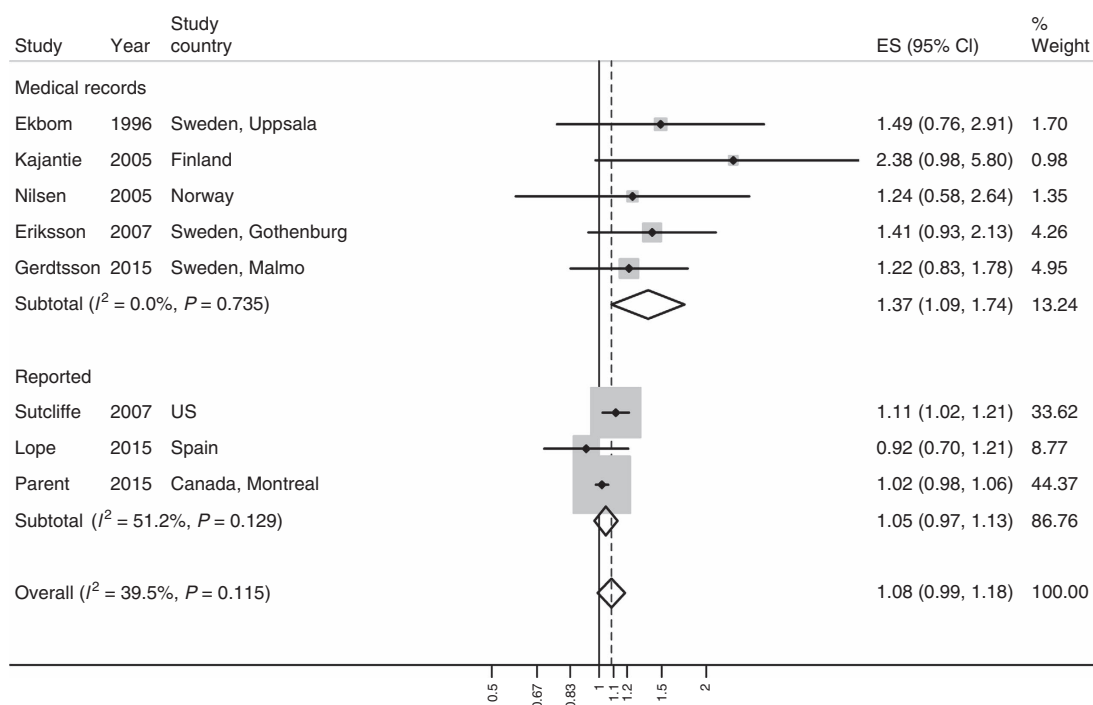


Figure 3. Birthweight (per kg) in relation to aggressive/lethal prostate cancer risk by birthweight source using a random-effects model ( $N = 8$ ).

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; Gertsson *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.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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