Supplementary Tables and Figures

A meta-analysis of individual participant data reveals an association between circulating levels of IGF-I and prostate cancer risk

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Supplementary Table S1. Study characteristics

Study (year)	Sample population	Location	Recruitment period	Prostate cancer ascertainment method	Nested case-control study characteristics	
					Ratio of case patients to control participants	Matching criteria and comments
Prospective Studies						
ATBC (2003)	Randomised trial of α-tocopherol and β-carotene among smokers	Finland	1985-1993	Cancer registry linkage, central review of medical records and specimens	1:4	Controls randomly selected from cohort
BLSA (2000)	Population-based cohort study of the physiology of aging	USA	1958-onward	Self-report with medical record review	1:2	Age (±2 year); follow-up time
BUPA (2006)	Health plan members	UK	1975-1982	Cancer registry and death registry linkage	1:3	Age (±1 year); duration of storage of the serum sample (±1 year). Controls required to be alive and without a cancer notification at time of case selection
CHS (2005)	Population-based cohort study	USA	1989-1993	Cancer registry linkage or self-report with hospital discharge confirmation	1:1	Frequency matched by age (within 3 years); race; year of entry; year of blood draw; control participants survived to same age as case patient
CLUE 1 (2001)	Population-based cohort study	USA	1974-onward	Cancer registry linkage	1:2	Age (±1 year); race; date of recruitment (±3 weeks)
EPIC Phase 1 and Phase 2 (2007, 2012)	Population-based cohort study	Europe	1991-2001	Cancer registry linkage; health insurance record linkage; Self-report with medical record review	1:1 except for the Umea centre which was 1:2	Study centre; age at blood draw (±6 months); time of blood draw (±1 hour); time between blood draw and last consumption of food/drink (<3, 3-6, >6 hours); length of follow-up
ERSPC (2004)	Population-based randomized trial of PSA screening	The Nether-lands	1991-2000	Diagnosis as part of trial protocol	1:1	Age (per 1-year group); PSA level at first visit (<2, 2-3, 3-4 µg/L); postal code
HPFS Phase 1 and Phase 2 (2005, 2010)	Cohort study of male dentists, optometrists, osteopathic physicians, podiatrists, pharmacists, and veterinarians	USA	1986	Self-report with medical record review	1:1	Year of birth (±1 year); date of recruitment (same year); time of blood collection (12 a.m.– 9 a.m., 9 a.m.–12 p.m., 12 p.m.–4 p.m., 4 p.m.–12 a.m.); PSA test before blood draw (y/n); season of blood draw; control participants had ≥1 screening PSA test after the date of blood draw
JACC (2010)	Population-based cohort study	Japan	1988-1990	Death certificate review	1:3	Study area; gender; age using baseline characteristics. All controls were alive, had not migrated, and were free of any cancer at the time of the matched case subject's death

KPMCP (1998)	Health plan members	USA	1964-1970	Record linkage to tumour registry	1:3	Same age
MCCS (2006)	Population-based cohort study	Australia	1990-1994	Cancer registry linkage	Not matched: designed as a case-cohort study	Not matched: designed as a case-cohort study
MEC (2010)	Population-based cohort study	USA	1993-1996 (Blood collection 2001-2006)	Cancer registry linkage	1:2	Geographical location (California/Hawaii); ethnicity; birth year (±1 year); date blood draw (±6 months); time blood draw (±2 hours); fasting status
NSHDC (2000, 2004)	Combination of a population-based intervention study to decrease cardiovascular disease and a population-based monitoring study of cardiovascular disease	Sweden	1985-onward	Cancer registry linkage	1:2	Age (±6 months); date of recruitment (±2 months); town or area of residency
PCPT (2013)	Randomised, placebo-controlled trial of finasteride and prostate cancer	USA	1994-1997	Diagnosed as part of trial protocol. Annual digital rectal examinations and PSA measurements. Biopsy if abnormal DRE or reported PSA level > 4.0 ng per. End-of-study prostate biopsy	1:1	Frequency matched: age (5-year age groups); PCPT treatment arm; positive family history for first-degree relative with prostate cancer. Controls required to have completed end of study biopsy procedure and had no evidence of prostate cancer.
PHS (1998, 2002, 2010)	Randomised trial of aspirin and β-carotene among physicians	USA	1982-onward	Self-report with medical record review	1:1-3	Age (±1 year and ±5 years for older men); smoking status (never, former, current); length of follow-up (Included both placebo and treatment arms, not stated whether cases and controls were matched by intervention/placebo group)
PLCO (2007)	Population-based randomised controlled multicentre trial of methods for early detection of cancer of the prostate, lung, colorectum and ovary.	USA	1993-2001	Medical and pathology record review after screening and self-report with medical record review	1:1 frequency matched	Age at cohort entry (5-year intervals); time since initial screening (1-year time window); and calendar year of cohort entry. All study participants selected from trial screening arm, i.e. offered PSA at recruitment and annually for 5 yrs, plus DRE at recruitment and annually for three years.
SU.VI.MAX (2005)	Population-based, double-blind, placebo-controlled, randomized trial of supplementation with antioxidant vitamins and minerals (vitamin C, α-tocopherol, β-carotene, selenium, and zinc)	France	1994	Self-reported in a monthly questionnaire on health-related events or detected through PSA screening of baseline bloods analysed at the end of trial. PSA values PSA ≥ 4.0 µg/L were followed up at participant's	1:4	Same age (All men randomized in the study were eligible)

				treating physician.		
Cross-sectional Studies						
ProtecT -Feasibility Phase (2004)	Cross-sectional study within the first phase of population-based PSA testing and randomised, controlled trial of treatments of localised prostate cancer	United Kingdom	1999-2002	Diagnosed as part of trial protocol. PSA test at recruitment followed by diagnostic biopsy if PSA ≥3ng/mL	1:1 stratum matched	2-year aged-band (age at PSA test); closest calendar date; GP/family practice (Controls had PSA below threshold [for first 12 months of study <3ng/ml or <4ng/ml if aged over 60 years, and thereafter PSA<ng/ml] or PSA above the threshold combined with at least 1 negative biopsy).
ProtecT (2012)	Cross-sectional study within a population-based PSA testing and randomised, controlled trial of treatments of localised prostate cancer	United Kingdom	2002-2009	Diagnosed as part of trial protocol. PSA test at recruitment followed by diagnostic biopsy if PSA ≥3ng/mL	1:1 stratum matched	5-year aged-band (age at PSA test); GP/family practice; time and season of blood draw due to timing of recruitment clinic. No overlap in study period with feasibility phase of ProtecT. (Controls had PSA<3ng/ml or raised PSA ≥3.0 ng/ml combined with at least 1 negative biopsy). Due to variation in measurements between assay kits, values are pre-adjusted for assay kit, age and sample storage time.

Abbreviations: ATBC, Alpha-Tocopherol Beta-Catotene Cancer Prevention Study; BLSA, Baltimore Longitudinal Study of Aging; CHS, Cardiovascular Health Study; BUPA, British United Provident Association Study; CLUE, Campaign Against Cancer and Stroke ("Give Us a Clue to Cancer") Study; EPIC, European Prospective Investigation into Cancer and Nutrition; ERSP, European Randomized Study of Screening for Prostate Cancer; HPFS, Health Professionals Follow-up Study; JACC, Japan Collaborative Cohort Study; KPMCP, Kaiser Permanente Medical Care Program; MCCS, Melbourne Collaborative Cohort Study; MEC, Multiethnic Cohort; NSHDC, Northern Sweden Health and Disease Cohort; PCPT, Prostate Cancer Prevention Trial; PHS, Physicians Health Study; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; ProtecT, Prostate Testing for Cancer and Treatment Study; PSA, prostate-specific antigen; SU.VI.MAX, SUpplémentation en VItamines et Minéraux AntioXydants.

Supplementary Table S2. Assay details for IGF-I, IGF-II, IGFBP-1, IGFBP-2 and IGFBP-3 measurements

Study (year)	Sample	IGF-I			IGF-II			IGFBP-1		
		Method (Manufacturer/ Laboratory)	Intra-assay CV	Inter-assay CV	Method (Manufacturer/ Laboratory)	Intra-assay CV	Inter-assay CV	Method (Manufacturer/ Laboratory)	Intra-assay CV	Inter-assay CV
Prospective Studies										
ATBC (2003)	Serum	ELISA (Diagnostic Systems Laboratories, Webster, Texas)	6.6% overall CV		NA			NA		
BLSA (2000, 2004)	Serum	RIA (Endocrine Sciences, Calabasas Hills, California)	4.6% to 20%	9.0% to 10%	RIA (Endocrine Sciences, Calabasas Hills, California)	4.9% to 9.6%	5.1% to 30%	NA		
BUPA (2006)	Serum	ELISA (Diagnostic Systems Laboratories, Webster, Texas)	Not given	Not given	ELISA (Diagnostic Systems Laboratories, Webster, Texas)	Not given	Not given	NA		
CHS (2005)	EDTA plasma	IRMA (Diagnostic Systems Laboratories, Webster, Texas)	3.0% to 3.8%	6.6% to 12.3%	NA			NA		
CLUE 1 (2001)	Serum	ELISA (Diagnostic Systems Laboratories, Webster, Texas)	Not given	Not given	Not published			Not published		
EPIC (2007, 2012)	Serum	ELISA (Diagnostic Systems Laboratories, Webster, Texas, phase 1 and phase 2 excluding Swedish samples) IDS-iSYS (Immuno-diagnostic Systems Ltd, Swedish samples for phase 2)	3.0% (phase 1) 4.4% (phase 2)	13.7% (phase 1) 3.2% (phase 2)	Not published			Not published		
ERSPC (2004)	Serum	IRMA (Diagnostic Systems Laboratories, Webster, Texas)	3.4%	Not given	NA			NA		
HPFS (2005, 2010)	Plasma	ELISA (Diagnostic Systems Laboratories, Webster, Texas)	<10% (batch 1998 to 2000, CV=13%).	Not given	NA			Not published		
JACC (2010)	Serum	IRMA (Daiichi Radioisotope Lab, Tokyo, Japan)	2.1% to 3.5%	Not given	IRMA (Daiichi Radioisotope Lab, Tokyo, Japan)	2.7% to 4.4%	Not given	NA		
KPMCP (1998)	Serum	RIA (Nichols Institute Diagnostics, San Clemente, California)	Not given	Not given	NA			NA		
MCCS (2006)	Plasma	ELISA (Diagnostic Systems Laboratories, Webster, Texas)	Not given	11.1%	NA			NA		
MEC (2010)	Serum	ELISA (Diagnostic Systems Laboratories, Webster, Texas)	2.1%	Not given	ELISA (Diagnostic Systems Laboratories, Webster, Texas)	1.8%	Not given	ELISA (Diagnostic Systems Laboratories, Webster, Texas)	2.2%	Not given
NSHDC (2000, 2004)	Plasma	IRMA (Immunotech, Marseille, France)	8.6% to 11.0%	13.8%	NA			IRMA (Diagnostic Systems Laboratories, Webster, Texas)	2.9%	Not given
PCPT (2013)	Serum	ELISA (Diagnostic Systems Laboratories, Webster, Texas)	Coefficients of variation 5.3% and 7.1% for 2 sets of controls		ELISA (Diagnostic Systems Laboratories, Webster, Texas)	Coefficients of variation 4.2% and 5.0% for 2 sets of controls		NA		

PHS (1998, 2002, 2010)	Plasma	ELISA (Diagnostic Systems Laboratories, Webster, Texas)	4.9% to 6.5%	Not given	ELISA (Diagnostic Systems Laboratories, Webster, Texas)	Not given	Not given	Not published
PLCO (2007)	Serum	ELISA (Diagnostic Systems Laboratories, Webster, Texas)	9% overall coefficient of variation		NA			NA
SU.VI.MAX (2005)	Plasma	Chemiluminescence (Diagnostic Products, Los Angeles, California)	5.3% (type of CV not reported)		IRMA (Immunotech, Marseille, France)	6.8% (type of CV not reported)		NA
Cross-sectional studies								
ProtecT -Feasibility Phase (2004)	Serum	ELISA (Diagnostic Systems Laboratories, Webster, Texas)	3%	15%	ELISA (Diagnostic Systems Laboratories, Webster, Texas)	5%	26%	NA
ProtecT (2012)	Serum	RIA (Professor Holly, in house assay)	ICC 0.86	ICC 0.66	RIA (Professor Holly, in house assay)	ICC 0.91	0.84	NA

For expansion of study names see Table 1.

Abbreviations: CV, coefficient of variation; EDTA, Ethylenediaminetetraacetic acid; EIA, enzyme immunoassay; IA, immunoassay, type unspecified; MS, mass spectrometry; NK, not known; RIA, radioimmunoassay; RRA, radioreceptor assay.

[a]Cases and controls were assayed in the same batch

Supplementary Table S2 (continued). Assay details for IGF-I, IGF-II, IGFBP-1, IGFBP-2 and IGFBP-3 measurements

Study (year)	IGFBP-2			IGFBP-3			Blinded	Same batch[a]
	Method (Manufacturer/ Laboratory)	Intra-assay CV	Inter-assay CV	Method (Manufacturer/ Laboratory)	Intra-assay CV	Inter-assay CV		
Prospective Studies								
ATBC (2003)	NA			ELISA (Diagnostic Systems Laboratories, Webster, Texas)	7.3% overall CV		Not given	Yes
BLSA (2000, 2004)	NA			RIA (Endocrine Sciences, Calabasas Hills, California)	5.1% to 13%	5.5% to 17%	Not given	Not given
BUPA (2006)	NA			ELISA (Diagnostic Systems Laboratories, Webster, Texas)	Not given	Not given	Yes	Yes
CHS (2005)	NA			IRMA (Diagnostic Systems Laboratories, Webster, Texas)	2.1% to 5.8%	4.1% to 7.1%	Not given	Not given
CLUE 1 (2001)	NA			ELISA (Diagnostic Systems Laboratories, Webster, Texas)	Not given		Yes	Yes
EPIC (Allen, 2007, Price 2012)	Not published			ELISA (Diagnostic Systems Laboratories, Webster, Texas)	5.3%	9.4%	Yes	Yes
ERSPC (2004)	NA			IRMA (Diagnostic Systems Laboratories, Webster, Texas)	3.9%	Not given	Yes	Yes
HPFS (2005, 2010)	NA			ELISA (Diagnostic Systems Laboratories, Webster, Texas)	<10%		Yes	Yes
JACC (2010)	NA			IRMA (Daiichi Radioisotope Lab, Tokyo, Japan)	3.1% to 4.2%	Not given	Yes	Not given
KPMCP (1998)	NA			NA			Not given	Not given
MCCS (2006)	NA			ELISA (Diagnostic Systems Laboratories, Webster, Texas)	9.5% coefficient of variation unspecified		Yes	Random assignment to batch, proportions of cases and controls were approximately equal for all batches
MEC (2010)	NA			ELISA (Diagnostic Systems Laboratories, Webster, Texas)	2.5%	Not given	Not given	Not given
NSHDC (2000, 2004)	RIA (Diagnostic Systems Laboratories, Webster, Texas)	2.5%	Not given	IRMA (Immunotech, Marseille, France)	3.6% to 4.9%	5.9% to 6.9%	Yes	Yes
PCPT (2013)	ELISA (Diagnostic Systems Laboratories, Webster, Texas)	Coefficients of variation 5.5% and 8.9% for 2 sets of controls		ELISA (Diagnostic Systems Laboratories, Webster, Texas)	Coefficients of variation 4.2% and 4.8% for 2 sets of controls		Yes	Not given
PHS (1998, 2002, 2010)	NA			ELISA (Diagnostic Systems Laboratories, Webster, Texas)	7.0% to 9.0%	Not given	Not given	Not given
PLCO (2007)	NA			ELISA (Diagnostic Systems Laboratories, Webster, Texas)	9% overall coefficient of variation		Not given	Yes
SU.VI.MAX (2005)	RIA (Diagnostic Systems Laboratories, Webster,	8.6% (type of CV not reported)		Chemiluminescence (Diagnostic Products, Los	6.3% (type of CV not reported)		Yes	Not given

	Texas)			Angeles, California)				
Cross-sectional Studies								
ProtecT -Feasibility Phase (2004)	RIA (Diagnostic Systems Laboratories, Webster, Texas)	5%	14%	RIA in-house	4%	14%	Yes	Yes
ProtecT (2012)	ELISA (Diagnostic Systems Laboratories)	ICC 0.95	ICC 0.81	RIA (Professor Holly, in house assay)	ICC 0.88	ICC 0.71	Yes	79%

Supplementary Table S3. Geometric mean (95% confidence interval) hormone and binding protein concentrations[a] by study and case-control status

Study	Case-control status	Geometric mean concentration (95% CI)				
		IGF-I, nmol/L	IGF-II, nmol/L	IGFBP-1, nmol/L	IGFBP-2, nmol/L	IGFBP-3, nmol/L
Prospective Studies						
ATBC	Case	18.0 (16.8-19.3)	N/A	N/A	N/A	83.9 (79.2-89.0)
	Control	17.7 (17.0-18.4)	N/A	N/A	N/A	79.0 (76.5-81.5)
BLSA	Case	17.9 (15.9-20.1)	22.6 (17.7-28.9)	N/A	N/A	97.3 (90.4-104.8)
	Control	17.8 (16.7-19.0)	40.9 (37.2-44.9)	N/A	N/A	94.7 (90.1-99.6)
BUPA	Case	15.2 (13.8-16.8)	93.0 (89.2-97.0)	N/A	N/A	99.9 (95.5-104.5)
	Control	15.0 (14.2-15.8)	89.7 (87.5-92.0)	N/A	N/A	95.2 (92.1-98.3)
CHS	Case	18.2 (16.9-19.5)	N/A	N/A	N/A	103.8 (99.2-108.6)
	Control	19.2 (17.9-20.6)	N/A	N/A	N/A	108.2 (103.7-112.9)
CLUE 1	Case	14.7 (12.8-16.9)	64.4 (58.2-71.4)	0.15 (0.09-0.24)	N/A	35.1 (31.5-39.1)
	Control	14.7 (13.4-16.1)	66.9 (61.9-72.4)	0.17 (0.13-0.23)	N/A	34.6 (32.2-37.1)
EPIC Phase 1	Case	22.0 (21.3-22.6)	N/A	N/A	N/A	129.9 (127.7-132.2)
	Control	21.2 (20.5-21.9)	N/A	N/A	N/A	128.6 (126.4-130.9)
EPIC Phase 2	Case	19.8 (19.5-20.1)	115.1 (112.5-117.6)	0.22 (0.20-0.24)	11.4 (10.9-11.8)	N/A
	Control	19.0 (18.7-19.3)	111.5 (109.0-114.1)	0.24 (0.22-0.26)	11.4 (10.9-11.8)	N/A
ERSPC	Case	16.3 (15.4-17.2)	N/A	N/A	N/A	123.4 (120.1-126.9)
	Control	16.3 (15.4-17.3)	N/A	N/A	N/A	125.1 (121.1-129.3)
HPFS Phase 1	Case	23.5 (22.9-24.0)	N/A	N/A	N/A	116.6 (114.0-119.2)
	Control	22.2 (21.7-22.8)	N/A	N/A	N/A	112.1 (109.4-114.8)
HPFS Phase 2	Case	28.1 (27.5-28.7)	N/A	0.63 (0.58-0.67)	N/A	130.4 (128.1-132.8)
	Control	27.2 (26.5-27.8)	N/A	0.65 (0.60-0.69)	N/A	126.7 (124.2-129.3)
JACC	Case	12.0 (8.8-16.2)	71.0 (65.8-76.5)	N/A	N/A	94.0 (85.2-103.8)
	Control	12.9 (11.2-14.9)	68.4 (65.3-71.8)	N/A	N/A	89.8 (84.8-95.2)
KPMCP	Case	20.2 (18.3-22.4)	N/A	N/A	N/A	N/A
	Control	20.6 (19.8-21.5)	N/A	N/A	N/A	N/A
MCCS	Case	21.8 (21.1-22.5)	N/A	N/A	N/A	105.0 (102.8-107.2)
	Control	21.8 (21.3-22.3)	N/A	N/A	N/A	103.6 (102.0-105.2)
MEC	Case	23.5 (22.8-24.3)	117.6 (114.3-121.1)	0.73 (0.66-0.80)	N/A	137.3 (133.8-141.0)
	Control	22.9 (22.4-23.5)	114.3 (111.8-116.8)	0.74 (0.69-0.79)	N/A	132.1 (129.3-134.9)
NSHDC	Case	26.4 (25.1-27.8)	N/A	1.23 (1.08-1.39)	17.5 (15.7-19.5)	83.3 (81.1-85.6)
	Control	25.3 (24.4-26.1)	N/A	1.33 (1.22-1.44)	16.5 (15.0-18.2)	80.1 (78.4-81.9)
PCPT	Case	26.4 (25.9-26.9)	228.4 (225.0-231.9)	N/A	15.3 (14.8-15.8)	139.2 (137.1-141.3)
	Control	26.1 (25.6-26.6)	223.9 (220.4-227.5)	N/A	14.0 (13.5-14.5)	136.7 (134.6-138.9)
PHS	Case	23.0 (22.4-23.6)	66.4 (62.9-70.2)	0.14 (0.13-0.16)	N/A	108.3 (106.4-110.2)
	Control	22.7 (22.1-23.3)	66.5 (63.8-69.4)	0.16 (0.14-0.18)	N/A	107.8 (105.7-109.8)
PLCO	Case	25.2 (24.4-26.0)	N/A	N/A	N/A	155.2 (152.2-158.2)
	Control	24.9 (24.2-25.6)	N/A	N/A	N/A	155.3 (152.7-157.9)
SU.VI.MAX	Case	19.4 (18.4-20.5)	141.3 (136.1-146.7)	N/A	6.3 (5.5-7.3)	139.8 (134.9-144.9)
	Control	18.7 (18.1-19.3)	142.4 (139.6-145.3)	N/A	6.5 (6.1-7.0)	142.6 (139.5-145.8)
Cross-sectional Studies						
ProtecT feas.	Case	17.1 (16.5-17.7)	65.8 (63.2-68.5)	N/A	13.4 (11.8-15.2)	120.5 (116.6-124.6)
	Control	16.3 (16.0-16.7)	56.7 (55.5-58.0)	N/A	15.5 (14.6-16.5)	109.8 (107.7-112.0)
ProtecT main	Case	20.4 (20.1-20.7)	100.8 (99.6-102.0)	N/A	18.8 (18.4-19.3)	155.4 (154.0-156.7)
	Control	20.4 (20.1-20.6)	97.3 (96.1-98.4)	N/A	18.1 (17.6-18.5)	148.3 (146.8-149.9)

[a]Geometric means (95% confidence intervals) for all cases and controls who are in complete matched case control sets and have measurements available for each analyte. For expansion of study names see Table 1. Abbreviations: N/A, data not available for this study.

Supplementary Table S4. Partial coefficients among controls between log-transformed concentrations of circulating hormones, binding proteins and other analytes, standardized within each study and adjusted for age at blood collection (5 age-groups).

	IGF-I	IGF-II	IGFBP-1	IGFBP-2	IGFBP-3
IGF-II	**0.40**†	-	-	-	-
IGFBP-1	**-0.13** [b]	**-0.16** [b]	-	-	-
IGFBP-2	**-0.09** [b]	**-0.20** [b]	**0.44** [b]	-	-
IGFBP-3	**0.57** [b]	**0.62** [b]	**-0.11** [b]	**-0.17** [b]	-
SHBG	**-0.13** [b]	**-0.26** [b]	**0.32** [b]	**0.42** [b]	**-0.26** [b]
Testosterone	0.004	**-0.13** [b]	**0.31** [b]	**0.32** [b]	**-0.08** [b]
Free testosterone	**0.11** [b]	0.03	**0.19** [b]	**0.09** [b]	**0.12** [b]
Estradiol	-0.03	**-0.11** [b]	<10 observations	0.07 [a]	-0.02
Free Estradiol	0.05[a]	0.04	<10 observations	**-0.15** [b]	**0.14** [b]
Insulin	-0.008	-0.08 [a]	**-0.49** [b]	**-0.39** [b]	-0.03
C-peptide	0.05[a]	0.07 [a]	**-0.47** [b]	**-0.20** [b]	**0.08** [b]

[a]Two -sided significance level *P* <0.05
[b]Two-sided significance level *P* <0.001

Supplementary Table S5. Odds ratios for prostate cancer associated with a doubling (rather than and 80 percentile increase as presented elsewhere) of concentration of IGFs among cases and their matched controls in all studies and in prospective studies

	All studies		Prospective Studies	
	OR (95% CI)	***P* trend**	**OR (95% CI)**	***P* trend**
IGF-I	1.12 (1.06-1.18)	<0.001	1.16 (1.09-1.23)	<0.001
IGF-II	1.21 (1.11-1.32)	<0.001	1.04 (0.92-1.18)	0.551
IGFBP-1	0.96 (0.93-1.00)	0.032	0.96 (0.93-1.00)	0.032
IGFBP-2	1.07 (1.02-1.11)	0.003	1.10 (1.02-1.19)	0.009
IGFBP-3	1.39 (1.28-1.51)	<0.001	1.27 (1.16-1.40)	<0.001

Supplementary Table S6. Odds ratios for prostate cancer by study-specific deciles of concentration of IGF-I and IGFBP-3 among cases and their matched controls in prospective studies

	IGF-I	IGFBP-3
	OR (95% CI)	**OR (95% CI)**
Decile		
1	1 (reference)	1 (reference)
2	1.12 (0.97- 1.28)	1.18 (1.01- 1.37)
3	1.13 (0.99- 1.31)	1.27 (1.09- 1.47)
4	1.09 (0.94- 1.25)	1.26 (1.08- 1.46)
5	1.20 (1.05- 1.38)	1.38 (1.18- 1.60)
6	1.16 (1.00- 1.33)	1.26 (1.08- 1.47)
7	1.28 (1.12- 1.48)	1.28 (1.10- 1.49)
8	1.23 (1.07- 1.42)	1.34 (1.15- 1.57)
9	1.30 (1.13- 1.50)	1.33 (1.14- 1.56)
10	1.43 (1.24-1.65)	1.39 (1.19-1.63)
***P* for trend**	<0.001	<0.001

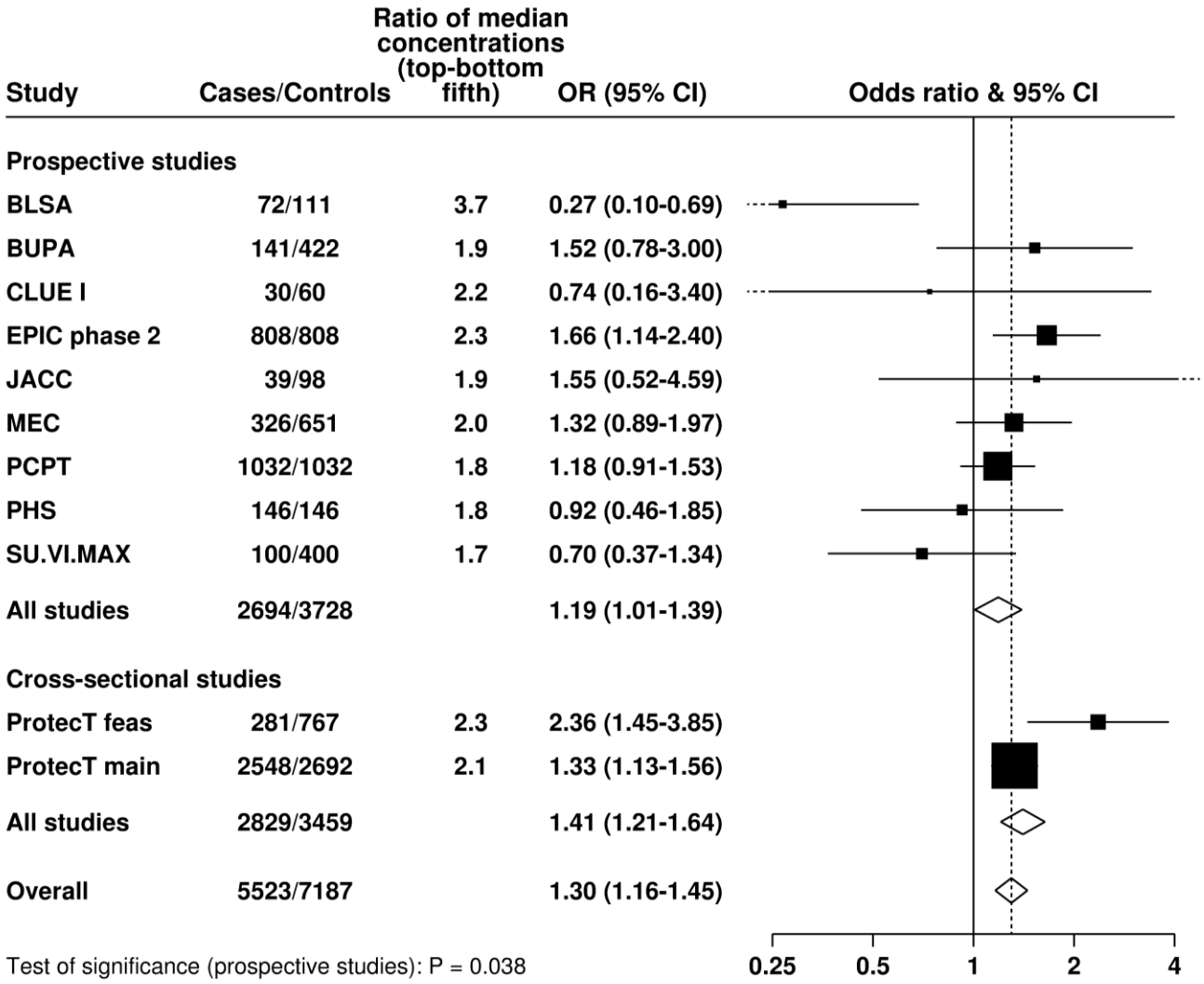
Supplementary Table S7. Odds ratios for prostate cancer associated with an 80 percentile increase in IGF concentration for selected pairs of IGFs, with mutual adjustment, among cases and their matched controls in prospective studies

	OR (95% CI)	*P* trend	Number of studies
IGF alone	1.29 (1.17-1.41)	<0.001	19
IGF-I adjusted for IGF-II	1.19 (1.00-1.42)	0.048	9
IGF-I adjusted for IGFBP-1	1.33 (1.11-1.58)	0.002	6
IGF-I adjusted for IGFBP-2	1.36 (1.13-1.63)	0.001	4
IGF-I adjusted for IGFBP-3	1.18 (1.04-1.33)	0.008	17
IGF-I adjusted for testosterone	1.26 (1.11-1.42)	<0.001	8
IGF-I adjusted for SHBG	1.22 (1.08-1.38)	0.001	8
IGF-II alone	1.19 (1.01-1.39)	0.038	9
IGF-II adjusted for IGF-I	1.09 (0.91-1.30)	0.4	9
IGF-II adjusted for IGFBP-3	0.97 (0.73-1.29)	0.8	8
IGF-II adjusted for testosterone	1.20 (0.98-1.47)	0.084	4
IGF-II adjusted for SHBG	1.19 (0.97-1.47)	0.1	4
IGFBP-1 alone	0.85 (0.73-1.00)	0.053	6
IGFBP-1 adjusted for IGF-I	0.90 (0.76-1.06)	0.2	6
IGFBP-1 adjusted for testosterone	0.98 (0.70-1.38)	0.9	2
IGFBP-1 adjusted for SHBG	1.00 (0.71-1.39)	1.0	2
IGFBP-2 alone	1.17 (1.05-1.31)	0.005	4
IGFBP-2 adjusted for IGF-I	1.35 (1.13-1.62)	0.001	4
IGFBP-2 adjusted for testosterone	1.71 (1.29-2.25)	<0.001	1
IGFBP-2 adjusted for SHBG	1.85 (1.39-2.48)	<0.001	1
IGFBP-3 alone	1.21 (1.09-1.34)	<0.001	17
IGFBP-3 adjusted for IGF-I	1.09 (0.96-1.24)	0.2	17
IGFBP-3 adjusted for IGF-II	1.17 (0.88-1.55)	0.3	8
IGFBP-3 adjusted for testosterone	1.28 (1.13-1.46)	<0.001	8
IGFBP-3 adjusted for SHBG	1.25 (1.09-1.42)	0.001	8

Supplementary Table S8. Odds ratios for prostate cancer by study-specific thirds of concentration of IGF-I and IGFBP-3, among cases and their matched controls in prospective studies

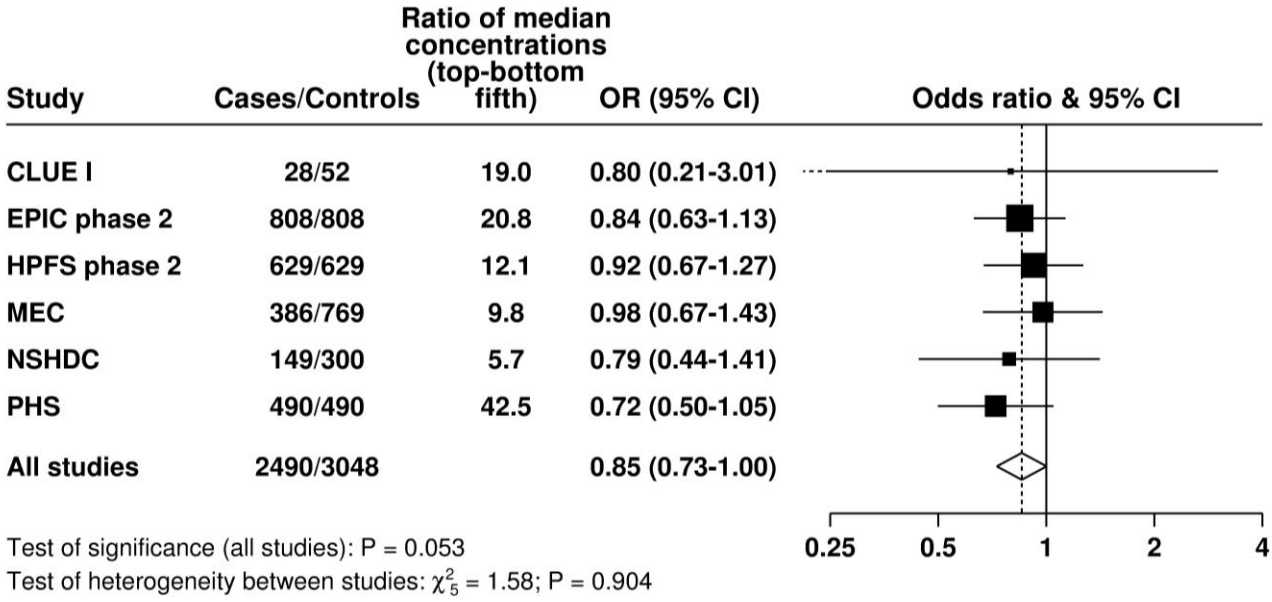
		Odds ratio (95% confidence interval)		
		Third of IGF-I		
		1	2	3
Third of IGFBP-3	**1**	1 (reference)	1.06 (0.93- 1.22)	1.11 (0.90- 1.37)
	2	1.16 (1.02- 1.33)	1.15 (1.03- 1.29)	1.16 (1.02- 1.32)
	3	1.17 (0.95- 1.43)	1.11 (0.97- 1.26)	1.26 (1.13- 1.40)
***P* for interaction**		0.6		

Supplementary Figure S1. Odds ratios for prostate cancer associated with an 80 percentile increase in IGF-II among all cases and their matched controls.

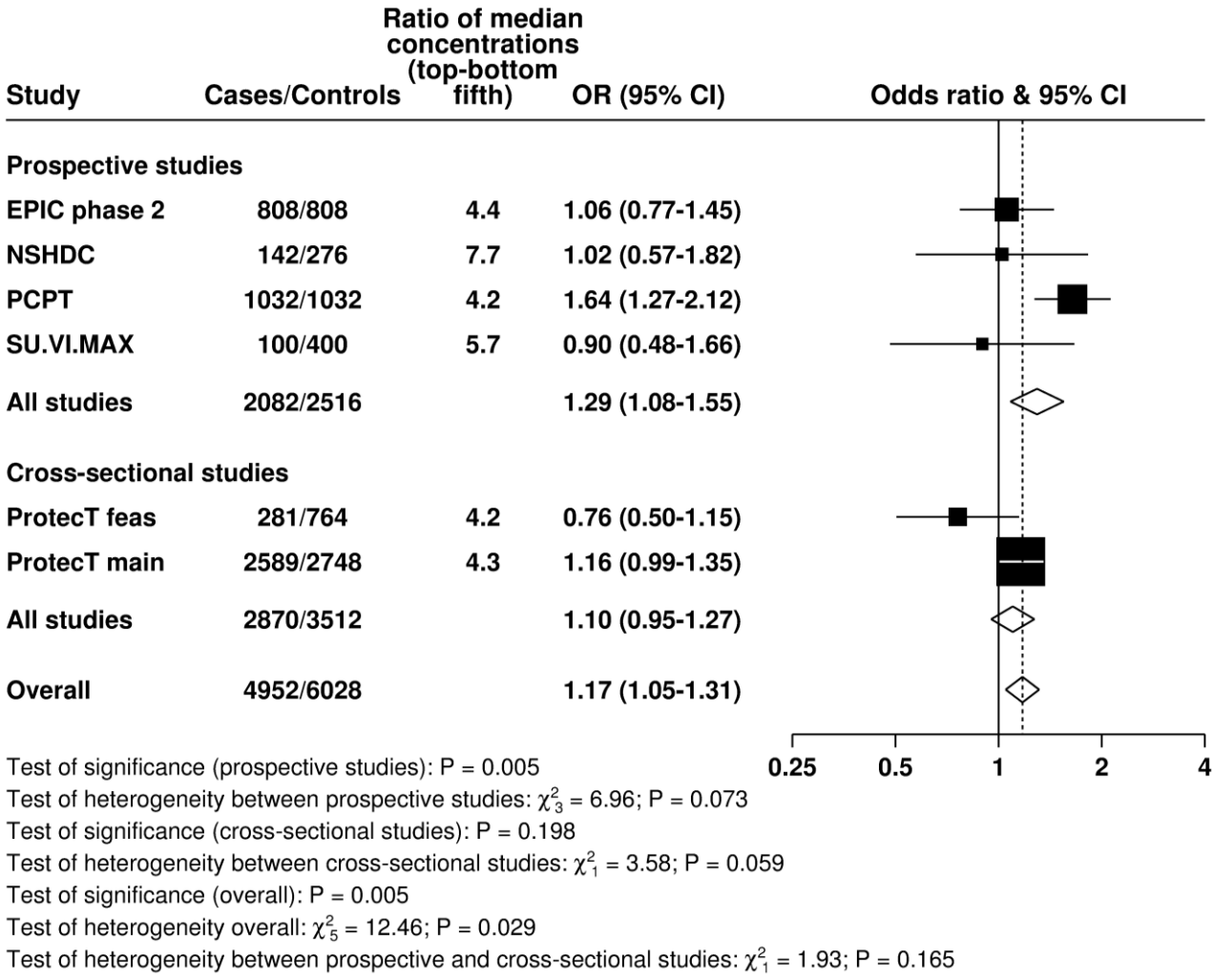


Test of significance (prospective studies): P = 0.038
Test of heterogeneity between prospective studies: $\chi^2_8 = 18.09$; P = 0.021
Test of significance (cross-sectional studies): P < 0.001
Test of heterogeneity between cross-sectional studies: $\chi^2_1 = 4.91$; P = 0.027
Test of significance (overall): P < 0.001
Test of heterogeneity overall: $\chi^2_{10} = 25.22$; P = 0.005
Test of heterogeneity between prospective and cross-sectional studies: $\chi^2_1 = 2.23$; P = 0.135

Supplementary Figure S2. Odds ratios for prostate cancer associated with an 80 percentile increase in IGFBP-1 among all cases and their matched controls (data are only available from prospective studies and not the cross-sectional PSA screening studies).

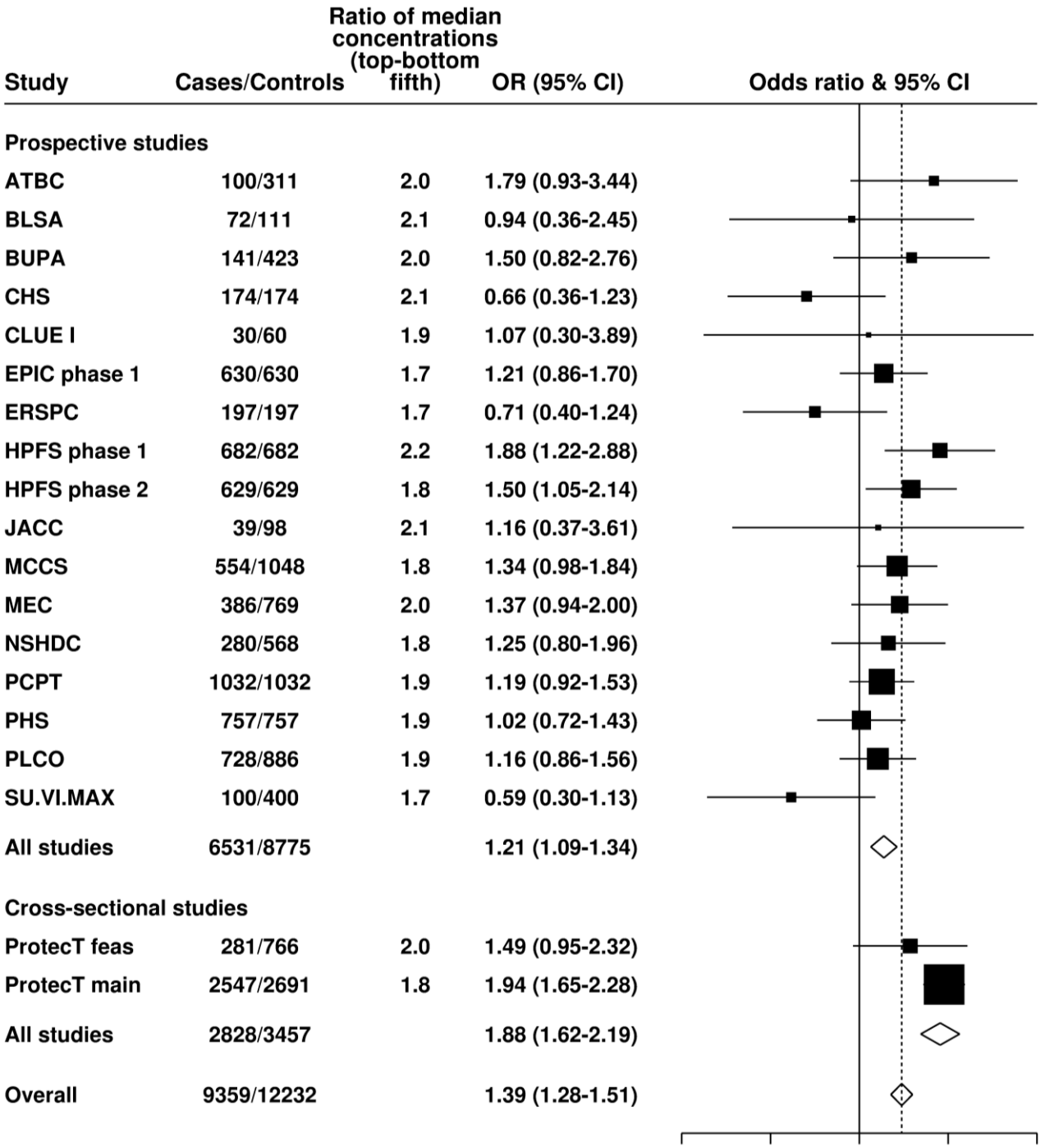


Supplementary Figure S3. Odds ratios for prostate cancer associated with an 80 percentile increase in IGFBP-2 among all cases and their matched controls.



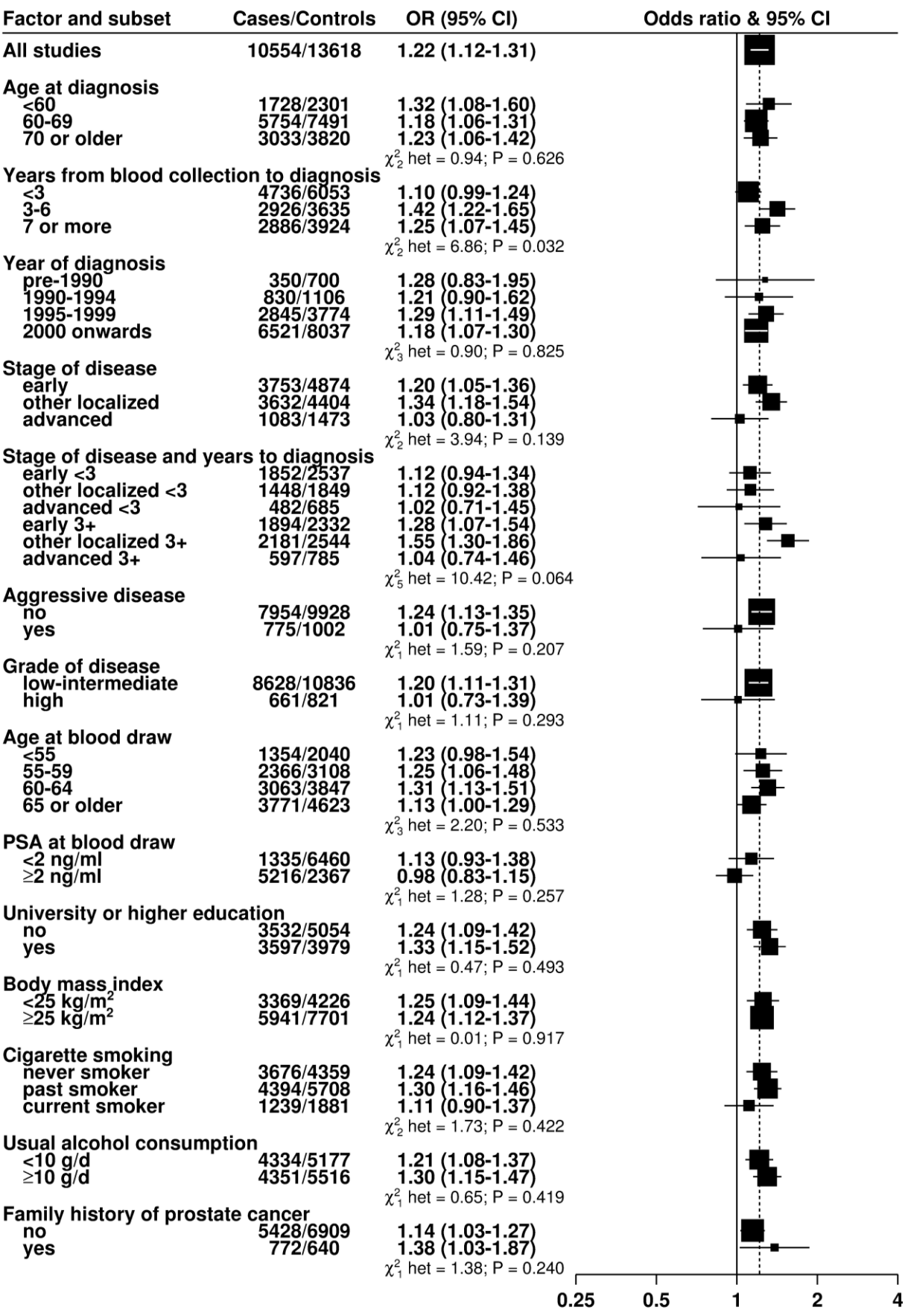
Test of significance (prospective studies): P = 0.005
Test of heterogeneity between prospective studies: $\chi^2_3 = 6.96$; P = 0.073
Test of significance (cross-sectional studies): P = 0.198
Test of heterogeneity between cross-sectional studies: $\chi^2_1 = 3.58$; P = 0.059
Test of significance (overall): P = 0.005
Test of heterogeneity overall: $\chi^2_5 = 12.46$; P = 0.029
Test of heterogeneity between prospective and cross-sectional studies: $\chi^2_1 = 1.93$; P = 0.165

Supplementary Figure S4. Odds ratios for prostate cancer associated with an 80 percentile increase in IGFBP-3 among all cases and their matched controls.

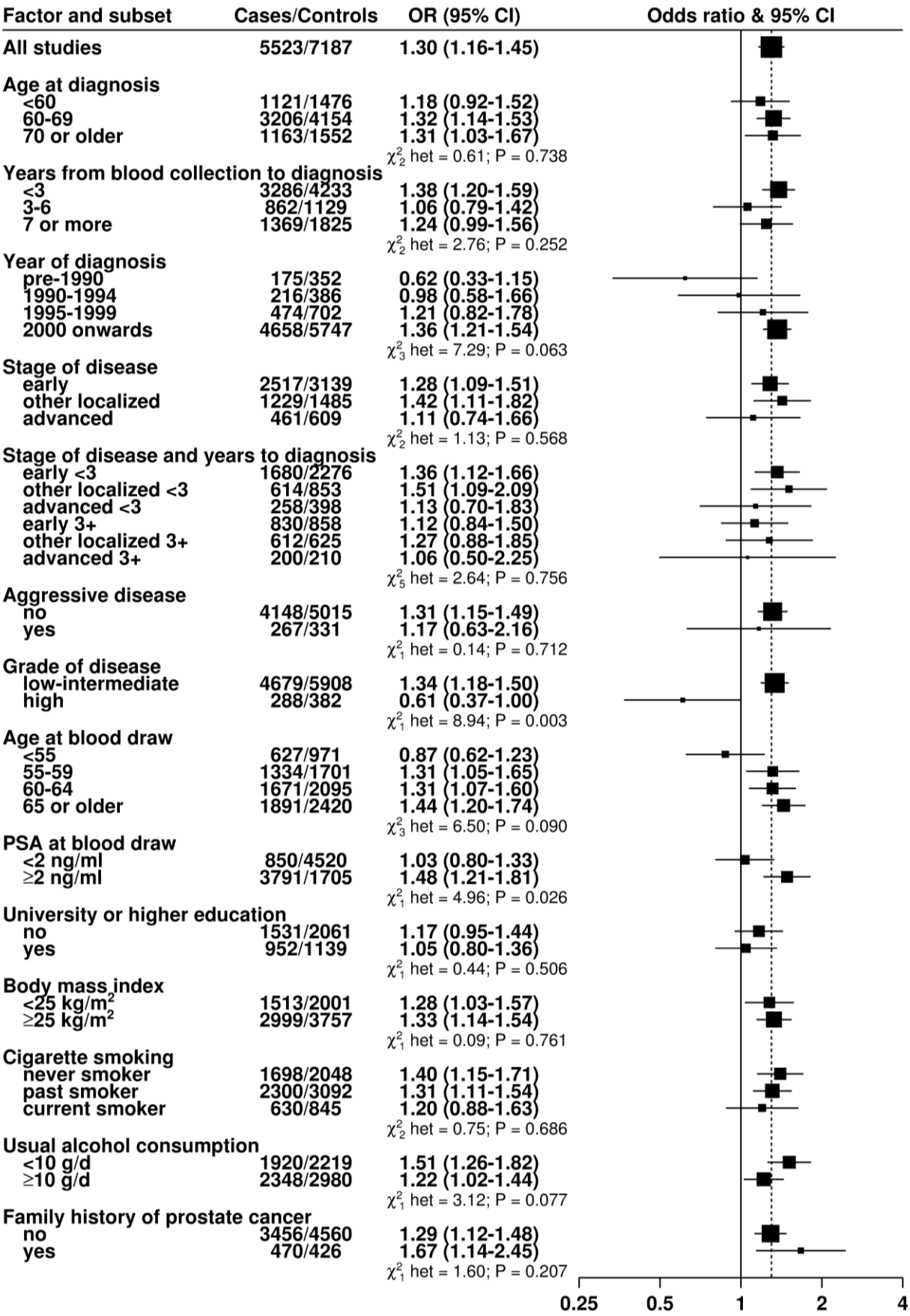


Test of significance (prospective studies): P < 0.001
Test of heterogeneity between prospective studies: $\chi^2_{16} = 21.69$; P = 0.153
Test of significance (cross-sectional studies): P < 0.001
Test of heterogeneity between cross-sectional studies: $\chi^2_1 = 1.19$; P = 0.276
Test of significance (overall): P < 0.001
Test of heterogeneity overall: $\chi^2_{18} = 45.22$; P < 0.001
Test of heterogeneity between prospective and cross-sectional studies: $\chi^2_1 = 22.34$; P < 0.001

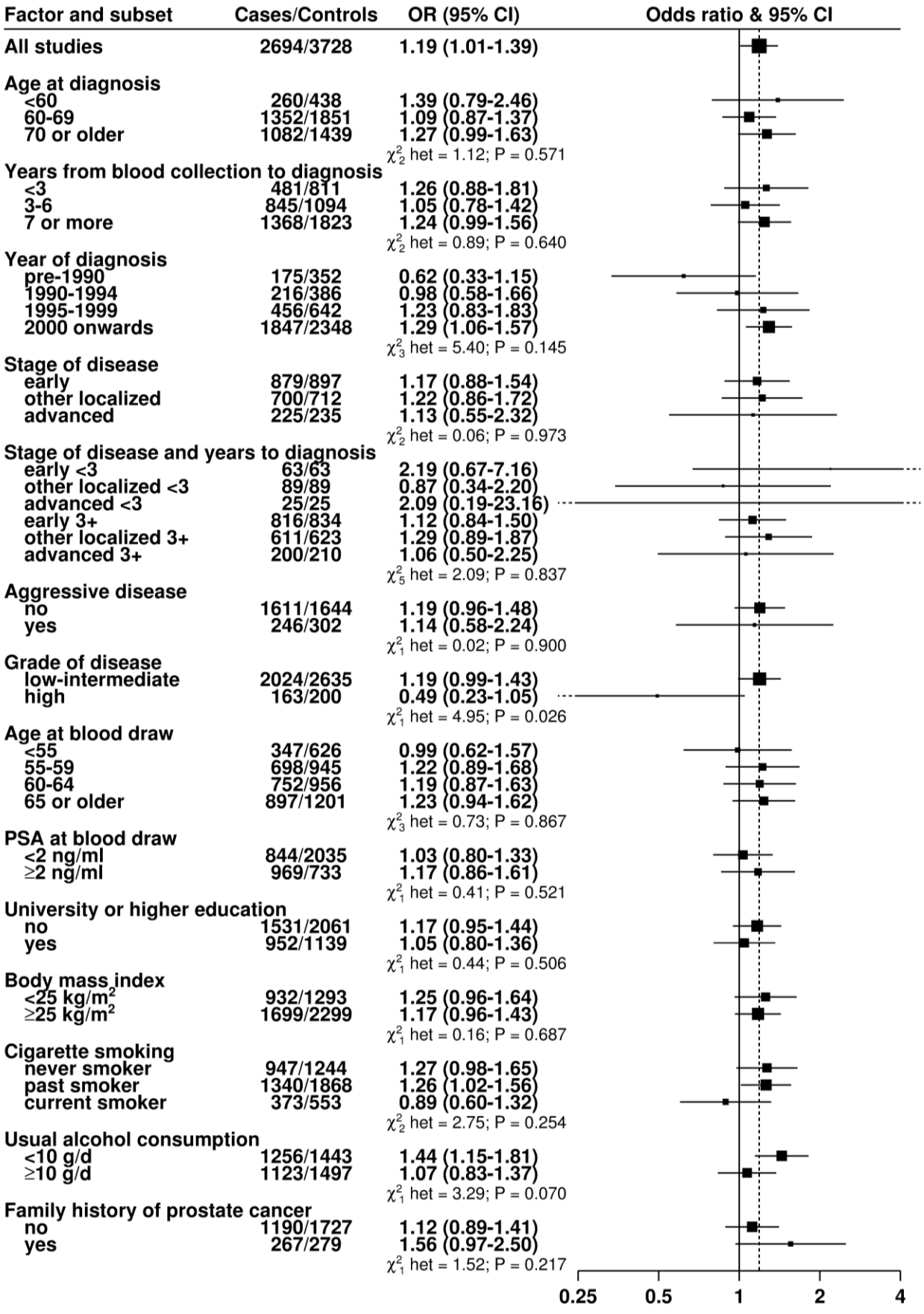
Supplementary Figure S5. Odds ratios for prostate cancer associated with an 80 percentile increase in IGF-I among cases and their matched controls, subdivided by various factors.



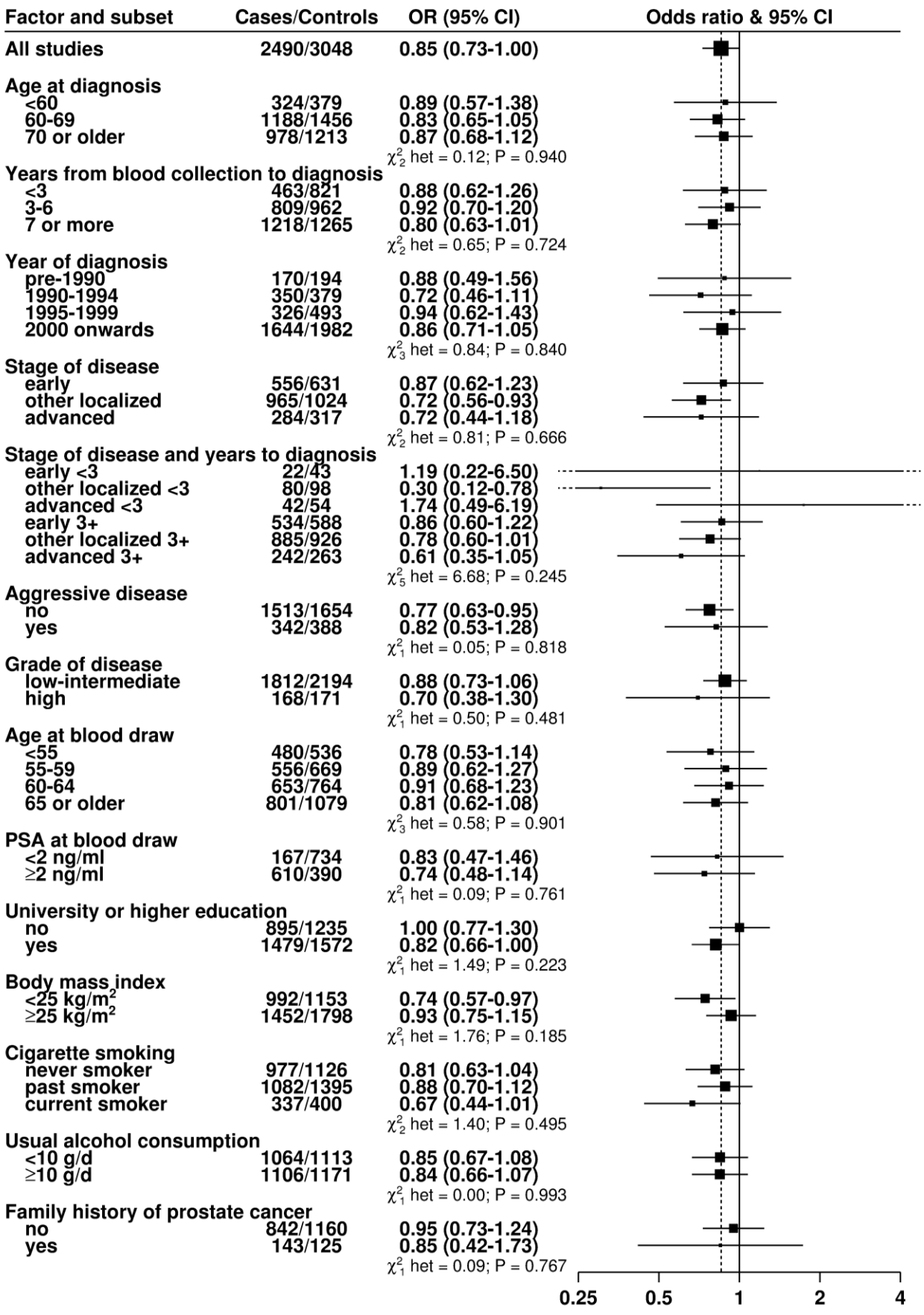
Supplementary Figure S6. Odds ratios for prostate cancer associated with an 80 percentile increase in IGF-II among cases and their matched controls, subdivided by various factors.



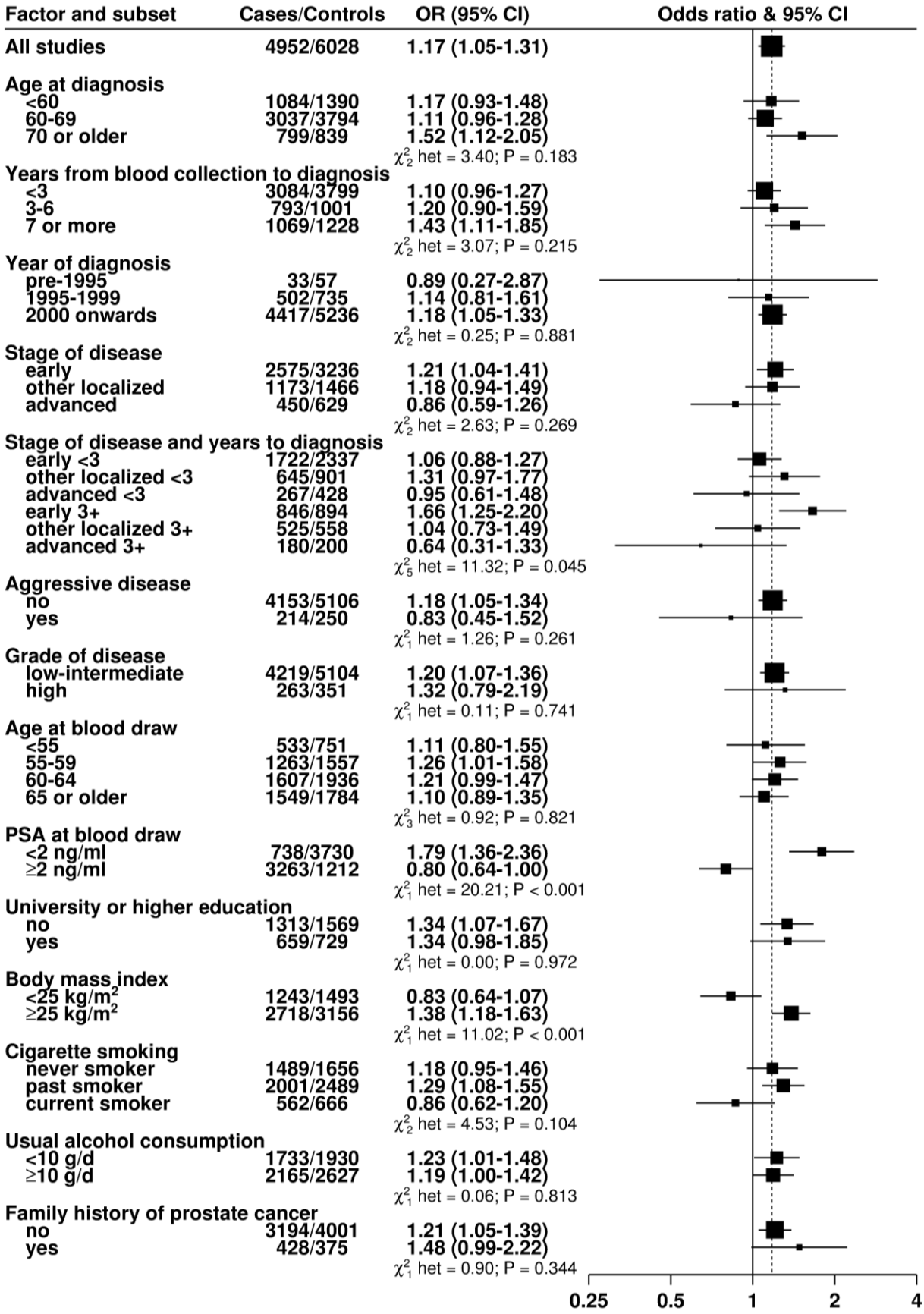
Supplementary Figure S7. Odds ratios for prostate cancer associated with an 80 percentile increase in IGF-II among all cases and their matched controls in prospectives studies, subdivided by various factors.



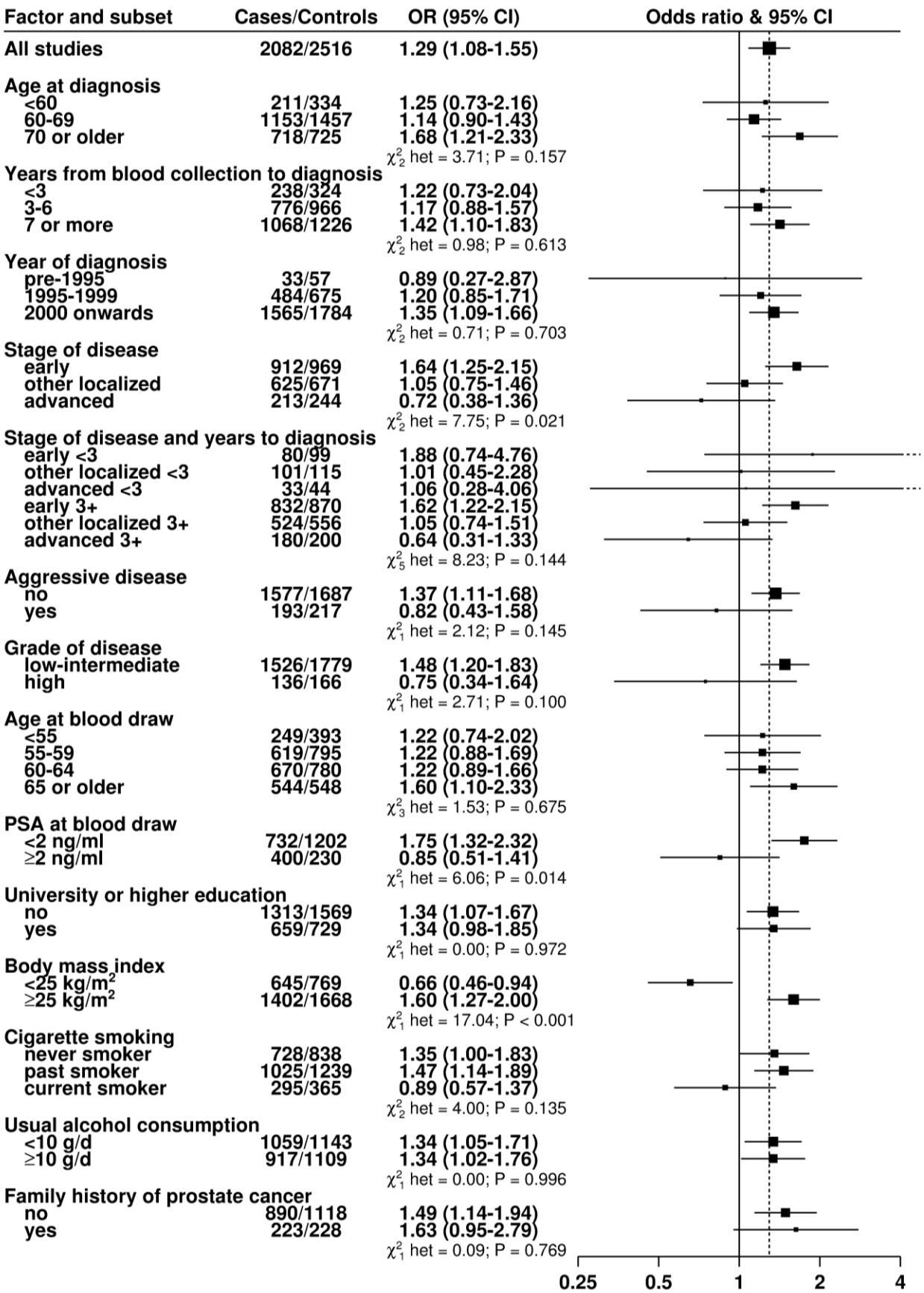
Supplementary Figure S8. Odds ratios for prostate cancer associated with an 80 percentile increase in IGFBP-1 among all cases and their matched controls in prospective studies, subdivided by various factors (data are only available for IGFBP-1 from prospective studies and not cross-sectional studies).



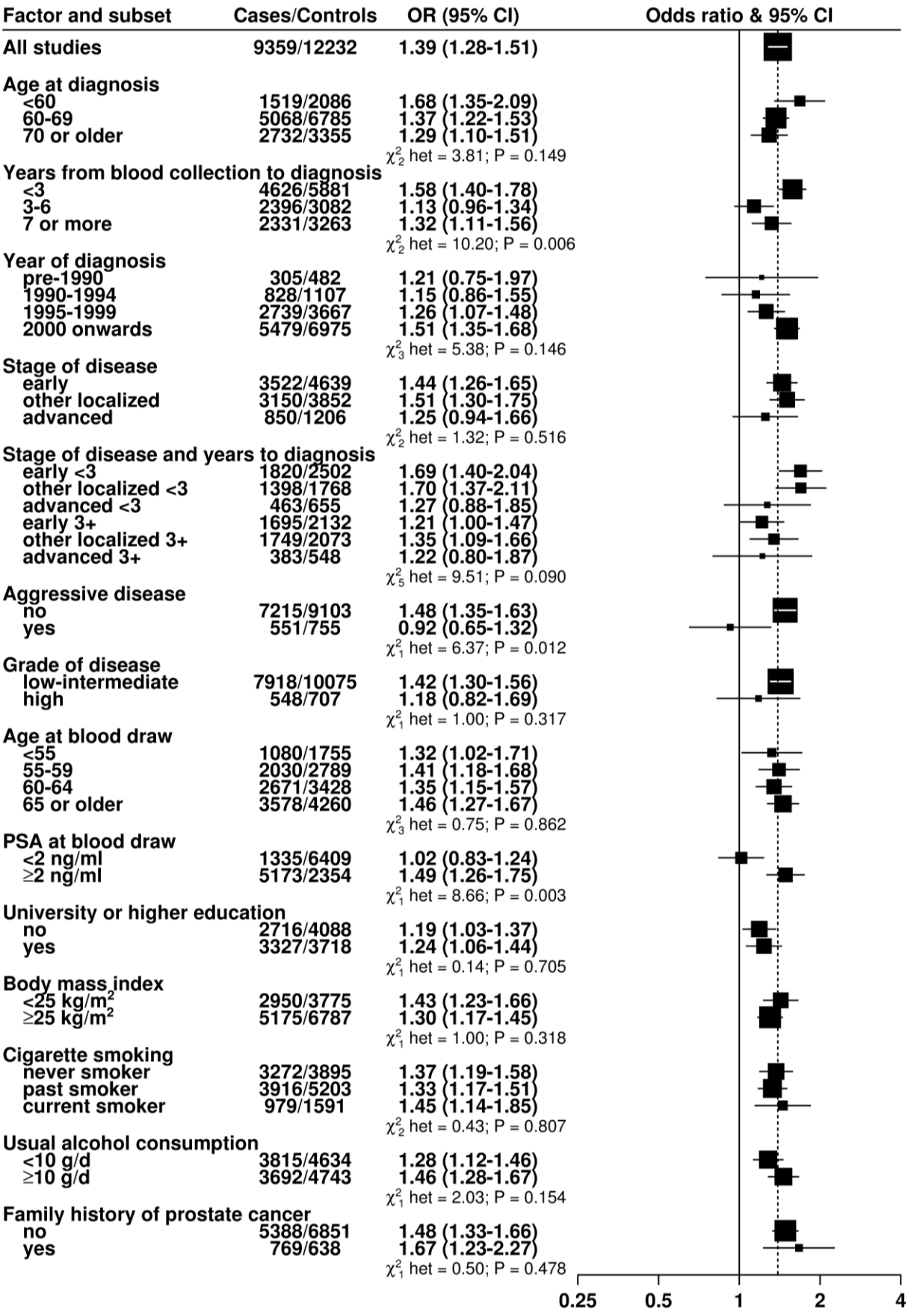
Supplementary Figure S9. Odds ratios for prostate cancer associated with an 80 percentile increase in IGFBP-2 among cases and their matched controls, subdivided by various factors.



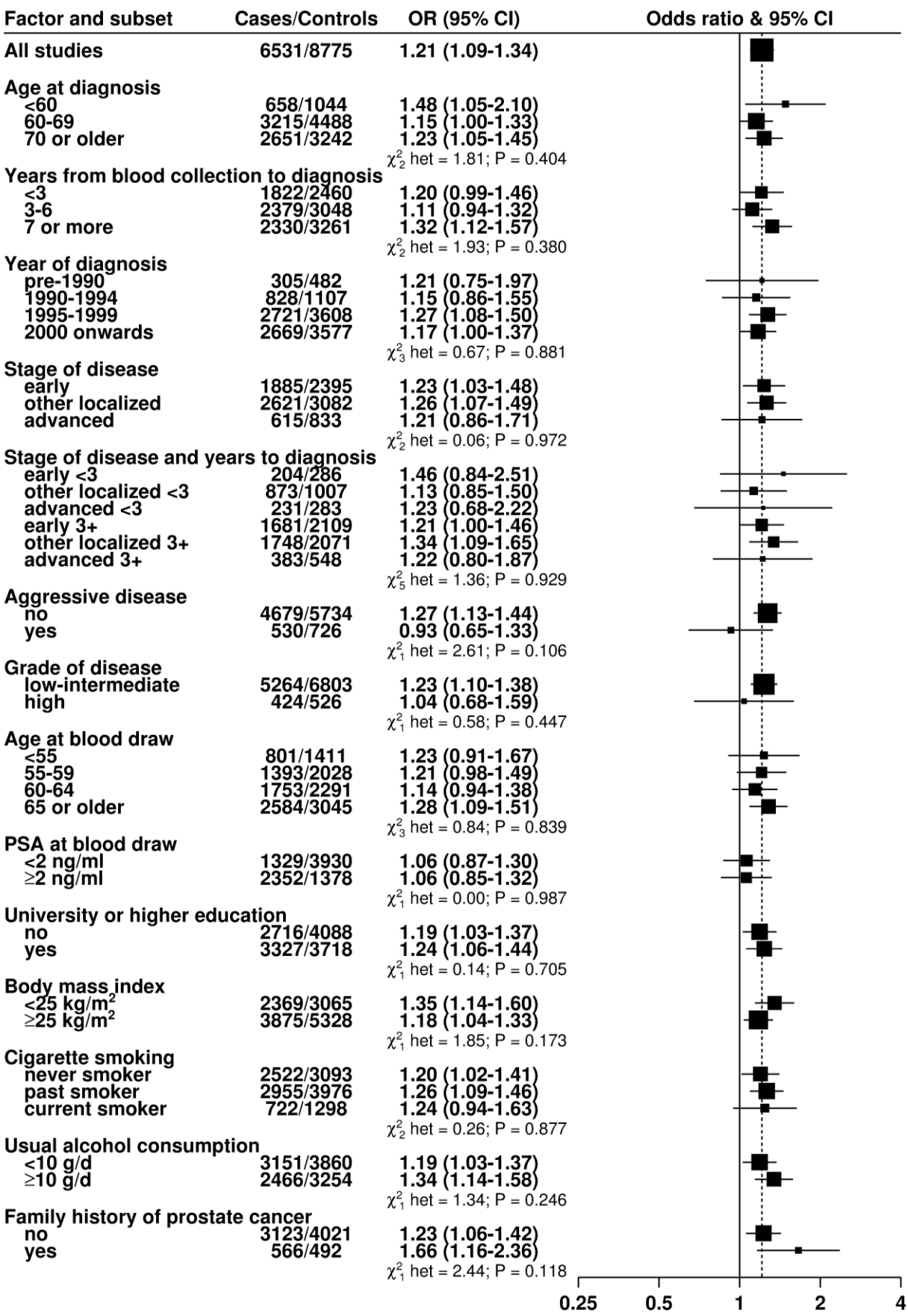
Supplementary Figure S10. Odds ratios for prostate cancer associated with an 80 percentile increase in IGFBP-2 among all cases and their matched controls in prospective studies, subdivided by various factors.



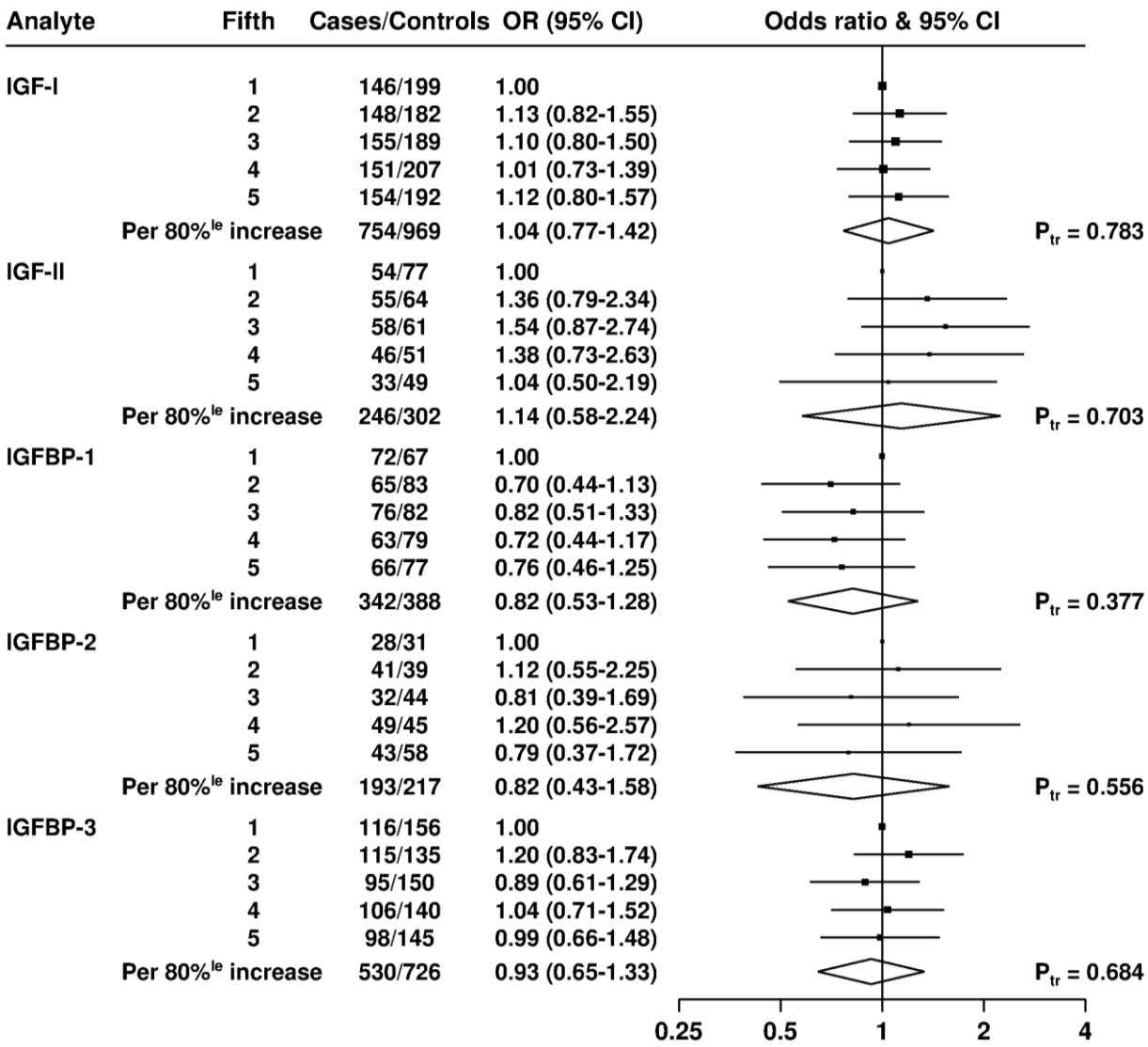
Supplementary Figure S11. Odds ratios for prostate cancer associated with an 80 percentile increase in IGFBP-3 among cases and their matched controls, subdivided by various factors.



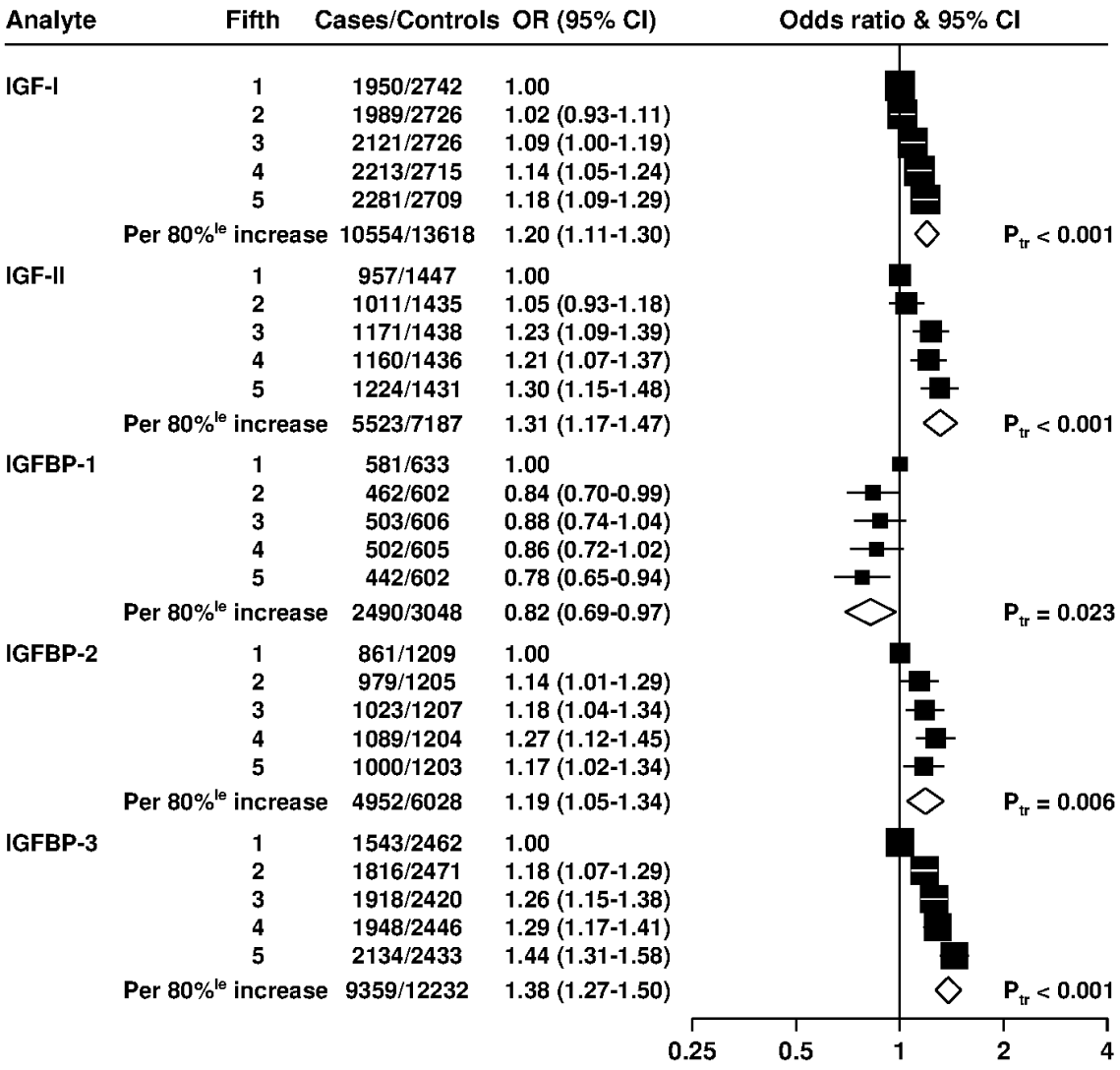
Supplementary Figure S12. Odds ratios for prostate cancer associated with an 80 percentile increase in IGFBP-3 among cases and their matched controls in prospective studies, subdivided by various factors.



Supplementary Figure S13. Odds ratios for aggressive prostate cancer by study-specific fifths of concentrations of selected insulin-like growth factors and their binding proteins among cases and their matched controls in prospective studies.



Supplementary FigureS14. Odds ratios for prostate cancer by study-specific fifth of selected IGFs among all cases and their matched controls, adjusted for exact age, marital status, educational level, smoking status, height and BMI.



Supplementary Figure S15. Odds ratios for prostate cancer by study-specific fifth of selected IGFs among cases and their matched controls in prospective studies, adjusted for exact age, marital status, educational level, smoking status, height and BMI.