

**Supplementary Data to “Family history and risk of bladder cancer: an analysis accounting for first- and second-degree relatives”**

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### Supplementary Materials and Methods

Totally 7 case-control and 1 case-cohort study (including 4,327 cases/8,948 non-cases) were included in the present study, with information on family history of bladder cancer and non-bladder cancer in either first- or second-degree relatives. These studies were originated from 5 countries including USA (4), Italy (2), Germany (1), Netherlands (1) and China (1). The detailed information of individual studies included in the present study are listed as following,

**USA:** 1) *Roswell Park Memorial Institute Case-control study on bladder cancer*, a hospital-based case-control study, retrospective data on dietary habits, family history and tobacco use were obtained from bladder cancer patients and age-matched controls admitted to Roswell Park Memorial Institute. Patients were ultimately diagnosed as having primary cancer of the bladder (ICD no. 188, ICD9). The question for assessing family history was asked as: “Do you have any blood relatives who were told they had cancer? (Including relationship to participants/type of cancer/age cancer diagnosed)”. 2) *Molecular Epidemiology of Bladder Cancer and Prostate Cancer*, a hospital-based case-control study, a nurse interviewer approached and interviewed participants using a standardized questionnaire. An epidemiological database was established and maintained to store patient data. Pathologic and laboratory data were collected, recorded, and linked to the epidemiological database. Medical charts and pathology reports were examined to ensure that the controls did not have a prior history of carcinoma. The question for assessing family history was asked as: “Do you have any family history of cancer”. 3) *Los Angeles bladder cancer Case-control study*, a population-based case-control study, identified non-Asian patients with histologically confirmed bladder cancer. In-person structured interviews were conducted in each subject’s home. The questionnaire requested information up to 2 years before the diagnosis of bladder cancer for case patients or 2 years before the diagnosis of cancer of the index case patient for the matched control subject. “Each subject was also asked if he/she has any family history of cancer, including type of cancer”. 4) *New Hampshire bladder cancer study*, a population-based case-control study, patients diagnosed with primary bladder cancers were identified through the New Hampshire State Cancer Registry. The control-group was randomly selected with a comparable sex and age distribution as the cancer cases from drivers’ license records (for those less than 65 years of ages) and from Medical enrolment files (for those 65 years of age and older). Those who agreed to take part in the study underwent an extensive in-person interview converting residence, occupation, medical history and, lifestyle factors (e.g., use of tobacco), and family history of cancer. The assessment of family history was self-report “first degree relatives with a history of bladder cancer”.

**Italy:** 1) *Brescia bladder cancer study*, a hospital-based case-control study, all diagnoses were histologically confirmed and classified according to the WHO classification. Controls were patients admitted in the same period as cases for urological non-neoplastic diseases known to be unrelated to the exposures under study. Cases and controls were interviewed by one interviewer, aware of the case-control status, who used a structured questionnaire that included questions on life-time occupational history, lifelong smoking habits, current alcohol and coffee consumption, education-level, and other information. The question for assessing family history was asked as: “Do you have any family history of cancer and their cancer types?”. 2) *Italian Case-control study on bladder cancer*, a hospital-based case-control

study, cases were confirmed by histological testing on tumor tissue specimen from biopsy or surgery, controls were matched to cases by study center, sex, and 5-year age groups. Trained interviewers administered a structured questionnaire to both cases and controls during their hospital stay. The questionnaire collected information on socio-demographic factors, lifestyle habits, diet in the 2 years before diagnosis/ interview, anthropometric measures 1 year prior to diagnosis/interview and at 30 and 50 years of age, problem-oriented medical history, and family history of cancer.

**Germany: *Dortmund Hörde study***, a hospital based case-control, questionnaires were sent out to all patients, containing questions about occupational history, occupational exposures to potential carcinogenic substances, smoking habits, diseases of relatives, and hobbies. Anthropometric data, staging and grading of the tumor, and additional diseases were reported by the physician. “The information of family history was obtained from the questionnaire and medical records reporting any disease of relative from the included participant”.

**Netherlands: *Netherlands Cohort Study on diet and cancer***, a case-cohort study, a subcohort was randomly sampled from the whole cohort after baseline exposure measurement and was followed up to obtain vital status information. Follow-up for incident cancer was established by record linkage to cancer registries and the Dutch database of pathology reports. All subjects completed a self-administered questionnaire on risk factors for cancer. The food-frequency section concentrated on habitual consumption during the year before the study began. The question for assessing family history was asked as: “Do you have any family history of cancer and what are the specific cancers?”.

**China: *Kaohsiung Bladder Cancer Case-control Study***, a hospital-based case-control, all of the bladder cancer cases were consecutive patients who were diagnosed and histologically confirmed in a medical center which neighbors the high incidence region of bladder cancer in the black-foot disease area, controls included ophthalmic patients with non-neoplastic and non-urological diseases, and normal renal and liver function. A trained interviewer questioned the cases and control subjects as outpatients or in the wards. Interviews were based on a structured questionnaire. The questionnaire covered demographic (e.g., sex, age, ethnicity), socioeconomic (e.g., educational level), family history, occupational, residential, smoking, alcoholic and non-alcoholic beverage, betel, and dietary variables. The question for assessing family history was asked in Chinese and translated to be: “Do you have any family members/relatives diagnosed with bladder cancer”, if yes, “what is the relationship of them to you (first-degree, second-degree, or third-degree)?”.

**Supplementary Table1** Additional Baseline Characteristic of the Participant Studies

Study Centre	No. of Participants (%)	Age at Baseline	Bladder Cancer cases (%)	% of Ever Smokers	Study Conducted Year	Study Design
Roswell Park Memorial Institute Case-control study on bladder cancer [1]	881	21–92	217	0.58	1957	Hospital-based case-control
Netherlands Cohort Study on diet and cancer [2]	5,632	55–70	940	0.67	1986	Case-cohort
Dortmund Hörde study [3]	426	22–100	193	0.68	1992	Hospital-based case-control
Molecular Epidemiology of Bladder Cancer and Prostate Cancer [4]	495	18–87	194	0.68	1994	Hospital-based case-control
Los Angeles bladder cancer Case-control study [5]	1,986	20–68	1,019	0.73	1987	Population-based case-control
New Hampshire bladder cancer study [6]	598	20–68	338	0.74	1992	Population-based case-control
Kaohsiung Bladder Cancer Case-control Study [7]	149	37–83	31	0.52	1996	Hospital-based case-control
Brescia bladder cancer study [8]	1,780	23–79	723	0.71	1994	Hospital-based case-control
Italian Case-control study on bladder [9]	1,328	25–84	672	0.75	2003	Hospital-based case-control

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**Supplementary Table 2** Bladder cancer risk for the combined effect of smoking status and family history in first- and second-degree relatives

Family History	Case (N)	Model 1		Model 2		Model 3	
		OR	95%	OR	95%	OR	95%
<b>Bladder Cancer</b>							
Never-smoker with non-family history	777	1.00		1.00		1.00	
Never-smoker with family history	27	2.05	1.19–3.52	1.73	0.91–3.30	1.67	0.88–3.17
Smoker with non-family history	3,433	2.59	2.36–2.84	2.04	1.82–2.29	1.65	1.45–1.87
Smoker with family history	128	4.61	3.34–6.37	3.50	2.41–5.09	3.43	2.39–4.91
<b>Non-bladder Cancer</b>							
Never-smoker with non-family history	698	1.00		1.00		1.00	
Never-smoker with family history	107	1.25	0.99–1.59	1.25	0.99–1.59	1.24	0.96–1.60
Smoker with non-family history	3,094	2.61	2.36–2.88	2.61	2.36–2.88	2.07	1.83–2.35
Smoker with family history	468	3.05	2.61–3.57	3.05	2.61–3.57	2.37	1.99–2.81

Estimates from multilevel logistic regression models adjusted for model 1: crude model without any adjustment; model 2: age, sex and ethnicity; model 3: additionally, adjust for smoking status, passive smoking and smoking pack-years.

Adjustments: age (years, continuous), sex (male or female), ethnicity (Caucasian or non-Caucasian), smoking status (never, former and current), pack-years was defined as the number of cigarettes smoked per day multiplied by the years of smoking (continuous).

Reference group was non-family history.

**Supplementary Table 3** Risk of bladder cancer by family history of cancer in first- and second-degree relatives (additionally adjust for passive smoking)

Family History	Case (N)	Model 1		Model 2		Model 3	
		OR	95%	OR	95%	OR	95%
<b>First-degree</b>							
<i>Urinary Bladder Cancer</i>							
No	4,210	1.00		1.00		1.00	
Yes	155	2.81	1.62–4.85	2.66	1.52–4.63	2.71	1.55–4.76
<i>Other Urologic Cancer</i>							
No	2,489	1.00		1.00		1.00	
Yes	55	1.99	1.06–3.75	1.73	0.91–3.28	1.81	0.95–3.48
<i>Non-urologic Cancer</i>							
No	3,792	1.00		1.00		1.00	
Yes	575	1.82	1.36–2.43	1.58	1.17–2.13	1.60	1.17–2.17
<b>Second-degree</b>							
<i>Urinary Bladder Cancer</i>							
No	1,461	1.00		1.00		1.00	
Yes	46	1.91	1.44–2.52	1.82	1.31–2.53	1.69	1.20–2.39
<i>Other Urologic Cancer</i>							
No	1,476	1.00		1.00		1.00	
Yes	16	1.26	0.90–1.76	1.25	0.89–1.76	1.26	0.89–1.78
<i>Non-urologic Cancer</i>							
No	1,387	1.00		1.00		1.00	
Yes	124	1.20	1.06–1.35	1.18	0.97–1.41	1.06	0.75–1.41

Estimates from multilevel logistic regression models adjusted for model 1: crude model without any adjustment; model 2: age, sex and ethnicity; model 3: additionally, adjust for smoking status, passive smoking and smoking pack-years.

Adjustments: age (years, continuous), sex (male or female), ethnicity (Caucasian or non-Caucasian), smoking status (never, current, or former), passive smoking (unknown, no, or yes), pack-years was defined as the number of cigarettes smoked per day multiplied by the years of smoking (continuous).

Reference group was non-family history.



**Supplementary Table 4** Risk of bladder cancer by family history of cancer in first- and second-degree relatives (excluding the case-cohort study)

Family History	Case (N)	Model 1		Model 2		Model 3	
		OR	95%	OR	95%	OR	95%
<b>First-degree</b>							
<i>Urinary Bladder Cancer</i>							
No	3,280	1.00		1.00		1.00	
Yes	105	2.16	1.55–2.99	1.91	1.29–2.85	1.81	1.21–2.70
<i>Other Urologic Cancer</i>							
No	1,570	1.00		1.00		1.00	
Yes	34	1.46	0.88–2.40	1.43	0.86–2.36	1.45	0.87–2.42
<i>Non-urologic Cancer</i>							
No	1,386	1.00		1.00		1.00	
Yes	380	1.66	1.27–2.54	1.43	1.07–2.12	1.57	1.08–2.55
<b>Second-degree</b>							
<i>Urinary Bladder Cancer</i>							
No	1,461	1.00		1.00		1.00	
Yes	39	2.91	1.61–5.27	2.82	1.55–5.13	2.90	1.59–5.31
<i>Other Urologic Cancer</i>							
No	1,397	1.00		1.00		1.00	
Yes	14	1.99	1.06–3.75	1.94	1.03–3.67	2.06	1.08–3.91
<i>Non-urologic Cancer</i>							
No	796	1.00		1.00		1.00	
Yes	66	1.30	0.89–1.90	1.30	0.88–1.91	1.28	0.87–1.89

Estimates from multilevel logistic regression models adjusted for model 1: crude model without any adjustment; model 2: age, sex and ethnicity; model 3: additionally, adjust for smoking status, passive smoking and smoking pack-years.

Adjustments: age (years, continuous), sex (male or female), ethnicity (Caucasian or non-Caucasian), smoking status (never, former and current), pack-years was defined as the number of cigarettes smoked per day multiplied by the years of smoking (continuous).

Reference group was non-family history.

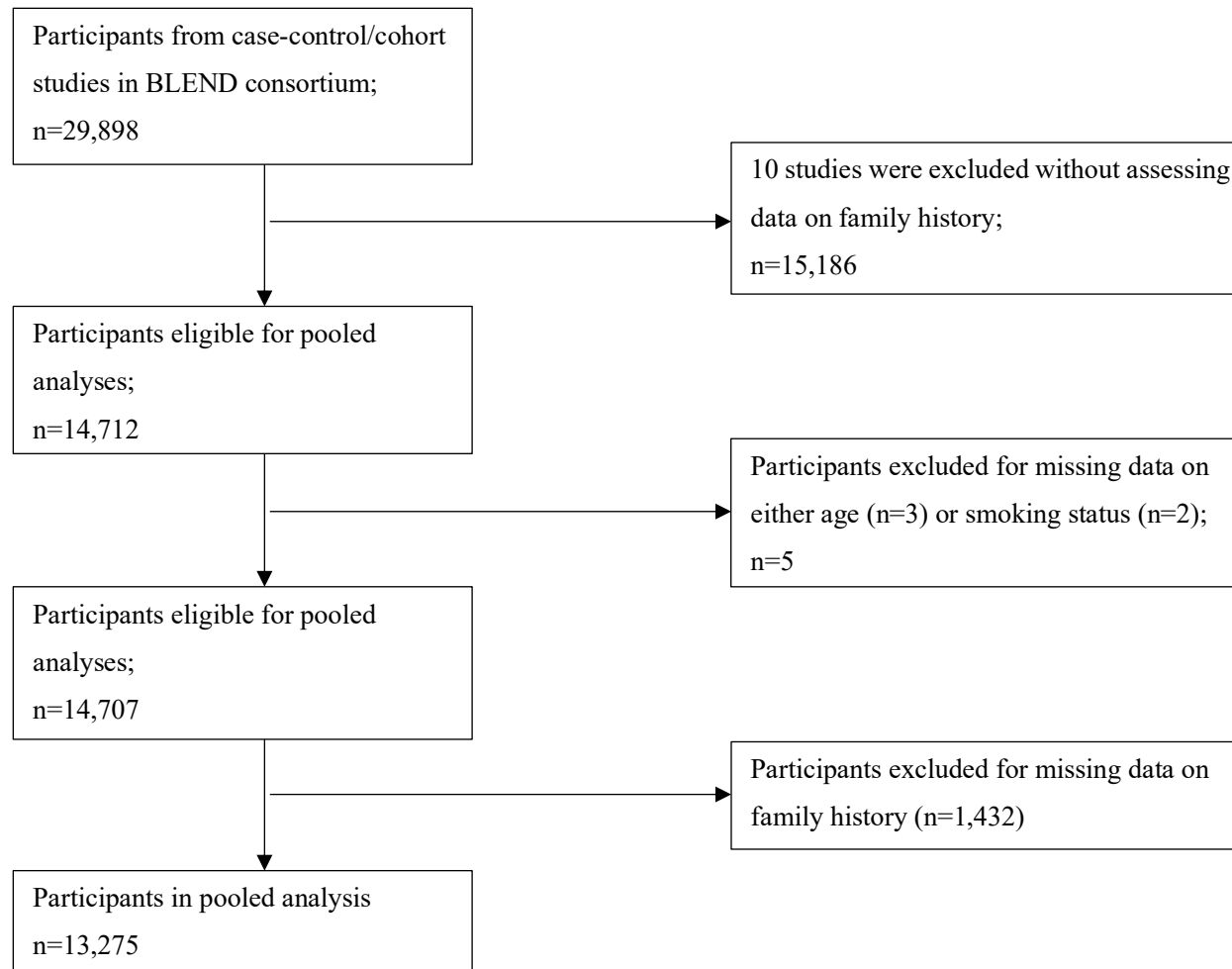
**Supplementary Table 5** Risk of bladder cancer by family history of cancer in first-degree relatives stratified for smoking status (excluding the case-cohort study)

Family History	Case (N)	Model 1		Model 2		Model 3	
		OR	0.95	OR	0.95	OR	0.95
<b>Bladder Cancer</b>							
Non-smoker with non-family history	648	1.00		1.00		1.00	
Non-smoker with family history	21	1.76	0.97–3.18	1.25	0.62–2.52	1.31	0.69–2.50
Smoker with non-family history	2,598	2.27	2.03–2.53	1.79	1.55–2.07	1.70	1.48–1.96
Smoker with family history	115	5.60	3.89–8.05	4.56	2.99–6.96	3.55	2.46–5.11
<b>Non-bladder Cancer</b>							
Non-smoker with non-family history	307	1.00		1.00		1.00	
Non-smoker with family history	64	1.28	0.99–1.66	1.44	1.11–1.88	1.41	1.08–1.83
Smoker with non-family history	1,100	2.51	2.20–2.85	2.17	1.89–2.49	1.81	1.54–2.12
Smoker with family history	106	2.68	2.23–3.21	2.29	1.90–2.76	1.92	1.57–2.36

Estimates from multilevel logistic regression models adjusted for model 1: crude model; model 2: age, sex and ethnicity; model 3: additionally, adjust for smoking status and smoking pack-years.

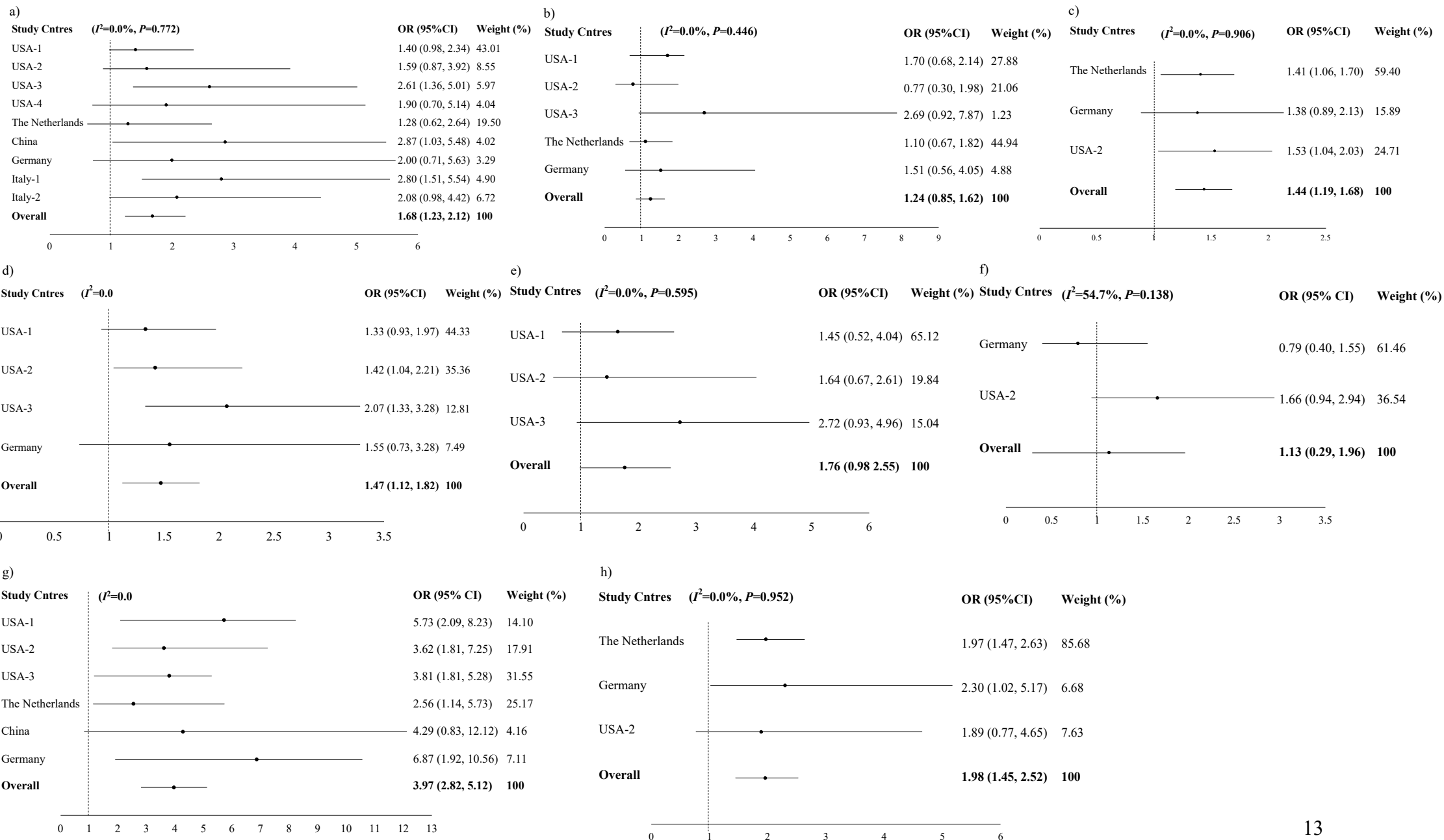
Adjustments: age (years, continuous), sex (male or female), ethnicity (Caucasian or non-Caucasian), smoking status (never, former and current), pack-years was defined as the number of cigarettes smoked per day multiplied by the years of smoking (continuous).

Reference group was non-family history.



**Supplementary Figure 1** Flow diagram of participants included in the statistical analyses on family history and bladder cancer risk

Abbreviation: BLEND, BLadder cancer Epidemiology and Nutritional Determinants; n, number.



**Supplementary Figure 2** Forest plots of Meta-analysis for family history with bladder cancer risk by each individual study

a) family history of bladder cancer in first-degree relatives; b) family history of other-urolologic-cancer in first-degree relatives; c) family history of non-urolologic cancer in first-degree relatives; d) family history of bladder cancer in second-degree relatives; e) family history of urolologic cancer in second-degree relatives; f) family history of non-urolologic cancer in second-degree relatives; g) smokers with family history vs. non-smokers without family history; h) smokers with family history vs. non-smokers without family history.

Abbreviation: CI, confidence interval; OR, odds ratio.

Diamond dots denote the odds ratios (ORs); Horizontal lines represent the 95% confidence intervals (CIs); Weights (grey squares) are from random effects analyses.

Adjustments: age (years, continuous), sex (male or female), ethnicity (Caucasian or non-Caucasian), smoking status (never, current, or former), pack-years was defined as the number of cigarettes smoked per day multiplied by the years of smoking (continuous).

The study centre was defined as: USA-1, Roswell Park Memorial Institute Case-control study on bladder cancer; USA-2, Molecular Epidemiology of Bladder Cancer and Prostate Cancer; USA-3, Los Angeles bladder cancer Case-control study; USA-4, New Hampshire bladder cancer study; Italy-1, Brescia bladder cancer study; Italy-2, Italian Case-control study on bladder; the Netherlands, Netherlands Cohort Study on diet and cancer; Germany, Dortmund Hörde study; China, Kaohsiung Bladder Cancer Case-control Study.