

SUPPLEMENTARY DATA

**Supplementary Table 1.** Hazard ratio (HR) and 95% confidence interval (CI) for metformin versus sulfonylurea monotherapy and cancer risk in the CPRD cohort by adjustment status.

Types of cancer	Multivariable-adjusted model 1*		Multivariable-adjusted model 2†		Multivariable-adjusted model 3‡	
	HR	95% CI	HR	95% CI	HR	95% CI
All types	1.06	0.98 - 1.14	1.03	0.96 - 1.11	0.96	0.89 - 1.04
Colorectal	1.00	0.83 - 1.20	1.00	0.83 - 1.21	0.92	0.76 - 1.13
Prostate	1.14	0.95 - 1.38	1.10	0.91 - 1.33	1.02	0.83 - 1.25
Lung	0.95	0.78 - 1.17	0.87	0.71 - 1.08	0.85	0.68 - 1.07
Postmenop. breast	1.16	0.93 - 1.44	1.15	0.92 - 1.44	1.03	0.82 - 1.31
Bladder	0.92	0.69 - 1.23	0.89	0.66 - 1.20	0.88	0.64 - 1.21
Esophageal	1.08	0.76 - 1.55	1.06	0.73 - 1.53	1.05	0.71 - 1.56
Melanoma	1.19	0.80 - 1.77	1.20	0.80 - 1.79	1.26	0.82 - 1.95
Leukaemia	0.93	0.64 - 1.36	0.94	0.64 - 1.39	0.86	0.57 - 1.31
Pancreatic	0.89	0.60 - 1.32	0.85	0.57 - 1.28	0.70	0.45 - 1.07
Gastric	1.01	0.65 - 1.55	1.00	0.64 - 1.57	0.96	0.60 - 1.56
NHL	1.08	0.68 - 1.71	1.04	0.65 - 1.66	0.94	0.57 - 1.55
Endometrial	1.70	0.95 - 3.03	1.67	0.93 - 3.02	1.38	0.74 - 2.57
Liver	0.97	0.58 - 1.63	1.02	0.60 - 1.72	0.85	0.49 - 1.48
Other types	1.12	0.91 - 1.37	1.09	0.89 - 1.34	1.00	0.80 - 1.25

Abbreviations: Postmenop, postmenopausal; NHL, Non-Hodgkin's Lymphoma

\* Intention-to-treat estimates from Cox proportional hazards models stratified for age and sex and adjusted for smoking status, BMI and alcohol consumption.

† Same as model 1 but further adjusted for use of aspirin or NSAIDs, use of statins and use of exogenous hormones in women (for colorectal, breast and endometrial cancer).

‡ Same as model 2 but further adjusted for diabetes duration and year of first antidiabetic prescription.

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**Supplementary Table 2.** Inverse probability weighted hazard ratio (HR) and 95% confidence interval (CI) for metformin versus sulfonylurea monotherapy and cancer risk in the CPRD cohort to correct for non-adherence at the initial treatment at years one, three and five\*

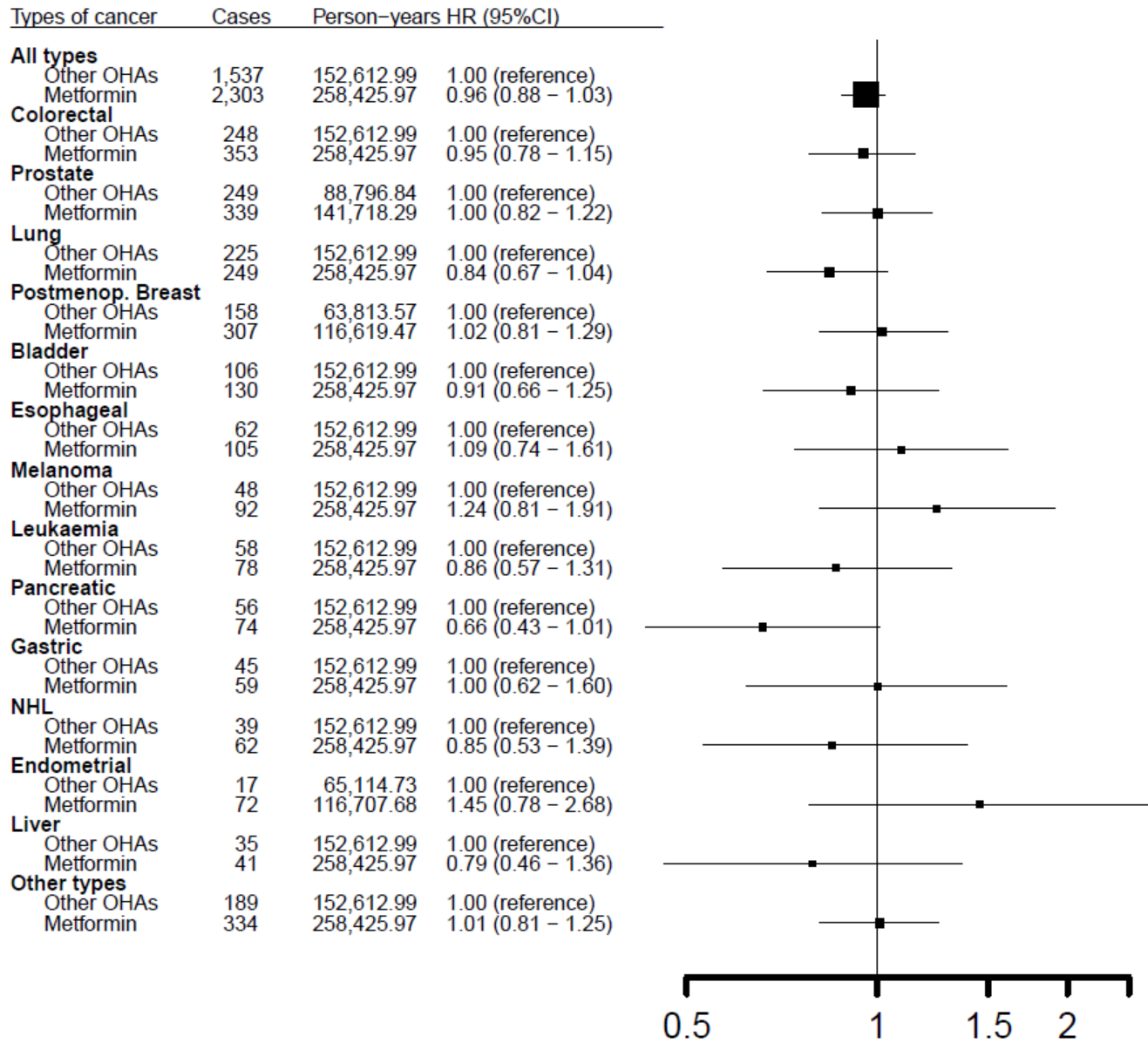
Types of cancer	First year		First three years		First five years	
	HR	95% CI	HR	95% CI	HR	95% CI
All types	0.96	0.89 - 1.03	0.95	0.87 - 1.04	0.94	0.85 - 1.04
Colorectal	0.92	0.76 - 1.12	0.89	0.71 - 1.12	0.88	0.68 - 1.13
Prostate	0.86	0.71 - 1.03	0.85	0.68 - 1.05	0.84	0.66 - 1.07
Lung	0.84	0.68 - 1.03	0.84	0.66 - 1.08	0.85	0.65 - 1.12
Postmenop. breast	1.13	0.91 - 1.41	1.33	1.02 - 1.74	1.47	1.07 - 2.02
Bladder	0.81	0.61 - 1.09	0.76	0.53 - 1.09	0.74	0.51 - 1.09
Esophageal	1.06	0.73 - 1.52	0.92	0.61 - 1.39	0.92	0.59 - 1.44
Melanoma	1.17	0.78 - 1.76	1.23	0.75 - 2.02	1.26	0.72 - 2.21
Leukaemia	0.84	0.58 - 1.24	0.71	0.45 - 1.11	0.69	0.43 - 1.12
Pancreatic	0.66	0.45 - 0.97	0.70	0.44 - 1.10	0.60	0.37 - 0.98
Gastric	0.91	0.57 - 1.45	0.83	0.49 - 1.42	0.83	0.47 - 1.47
NHL	0.91	0.58 - 1.43	0.93	0.54 - 1.58	0.90	0.49 - 1.66
Endometrial	2.51	1.36 - 4.65	2.04	1.01 - 4.11	2.29	0.98 - 5.38
Liver	1.06	0.60 - 1.87	0.95	0.47 - 1.95	0.78	0.36 - 1.68
Other types	1.10	0.89 - 1.36	1.10	0.86 - 1.41	1.10	0.83 - 1.46

Abbreviations: Postmenop, postmenopausal; NHL, Non-Hodgkin's Lymphoma

\* All statistical models are from intention-to-treat Cox proportional hazards regression stratified for age and sex and adjusted for smoking status, BMI, alcohol consumption, use of aspirin or NSAIDs, use of statins, use of exogenous hormones in women (for colorectal, breast and endometrial cancer), diabetes duration and year of first antidiabetic prescription.

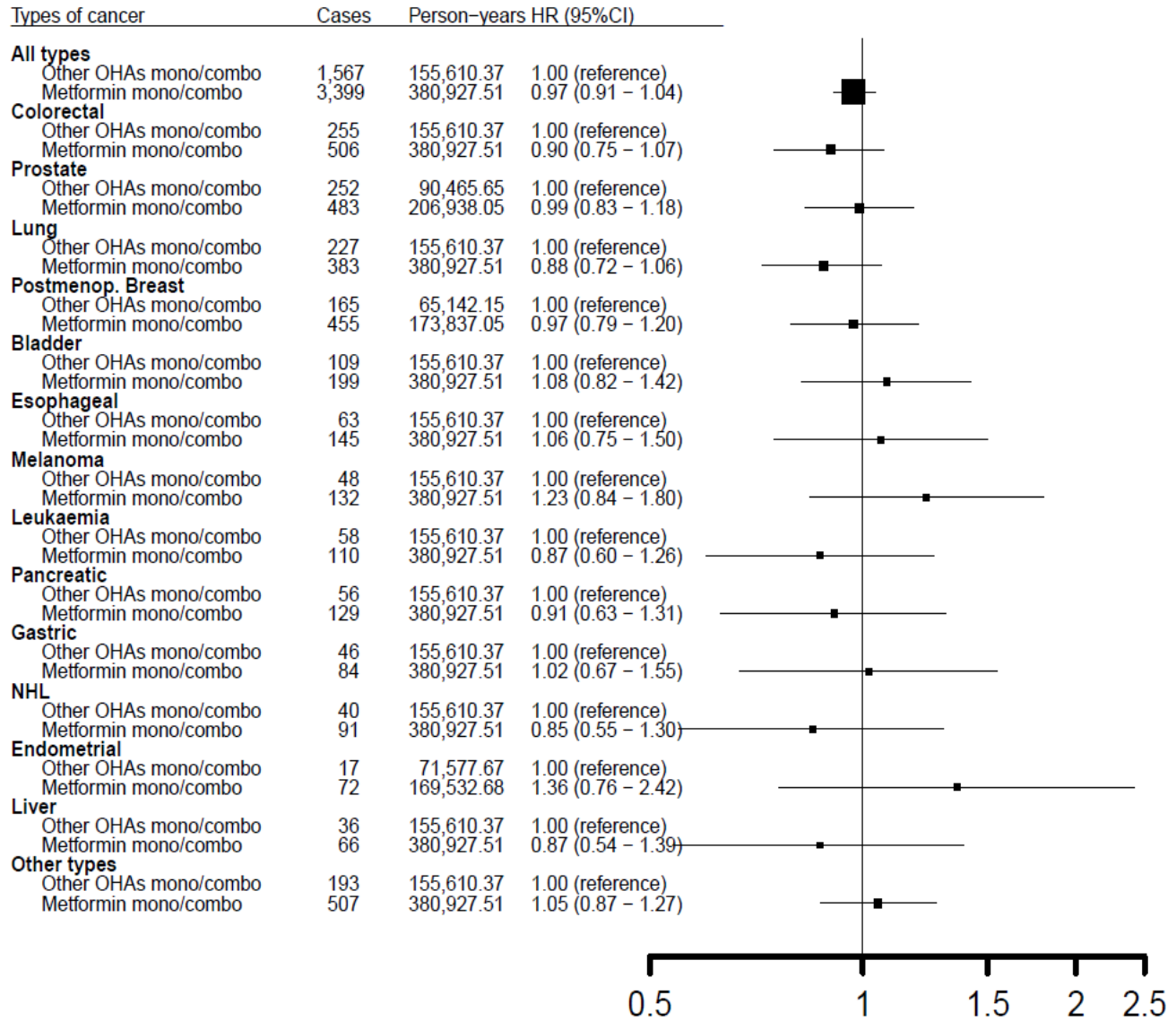
SUPPLEMENTARY DATA

**Supplementary Figure 1.** Multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) for the association between initiators of metformin monotherapy and initiators of other oral hypoglycemic agents monotherapy and cancer risk using the intention-to-treat principle in the CPRD.



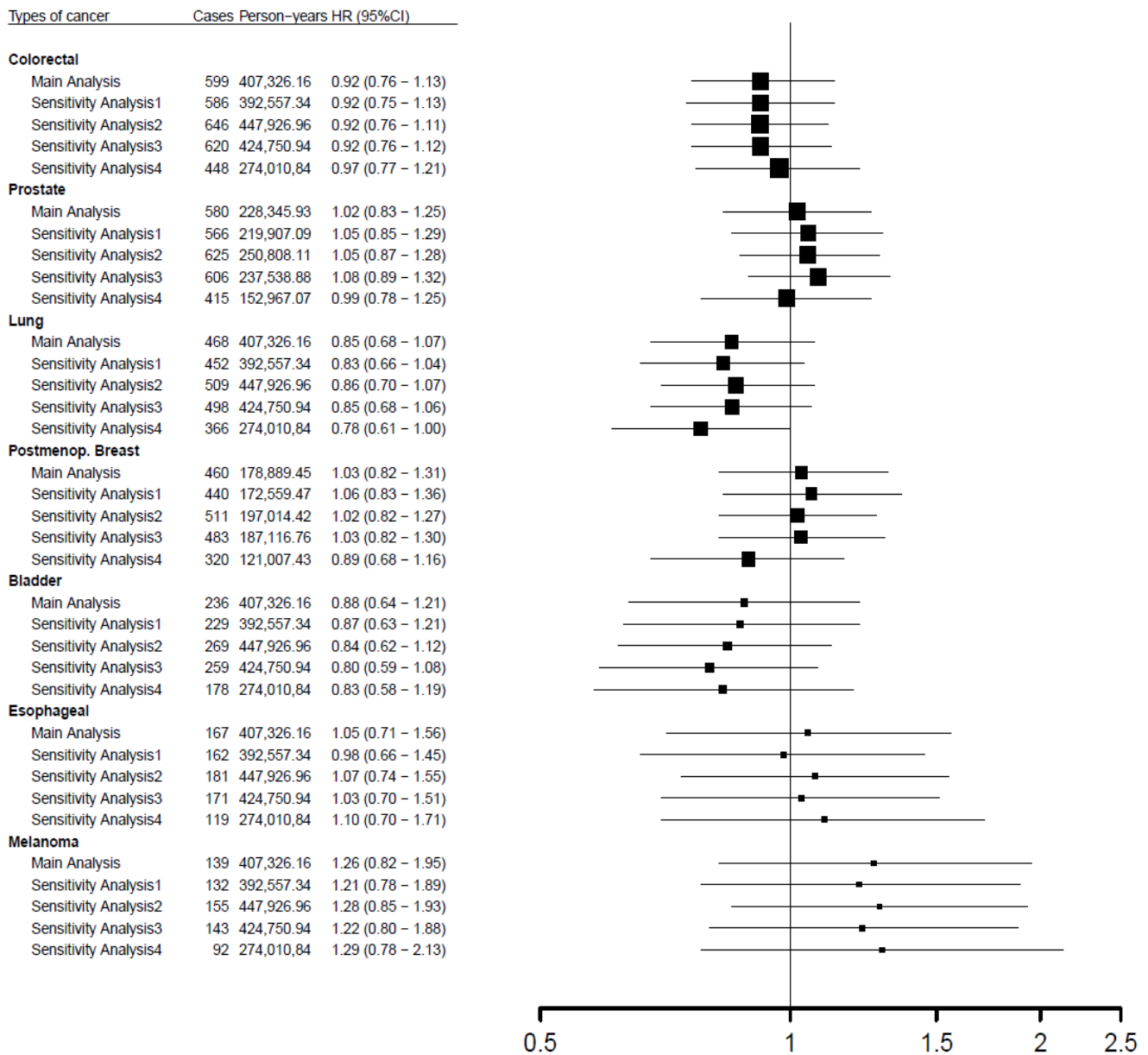
SUPPLEMENTARY DATA

**Supplementary Figure 2.** Multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) for the association between initiators of metformin mono or combination therapy and initiators of other oral hypoglycemic agents mono or combination therapy and cancer risk using the intention-to-treat principle in the CPRD.



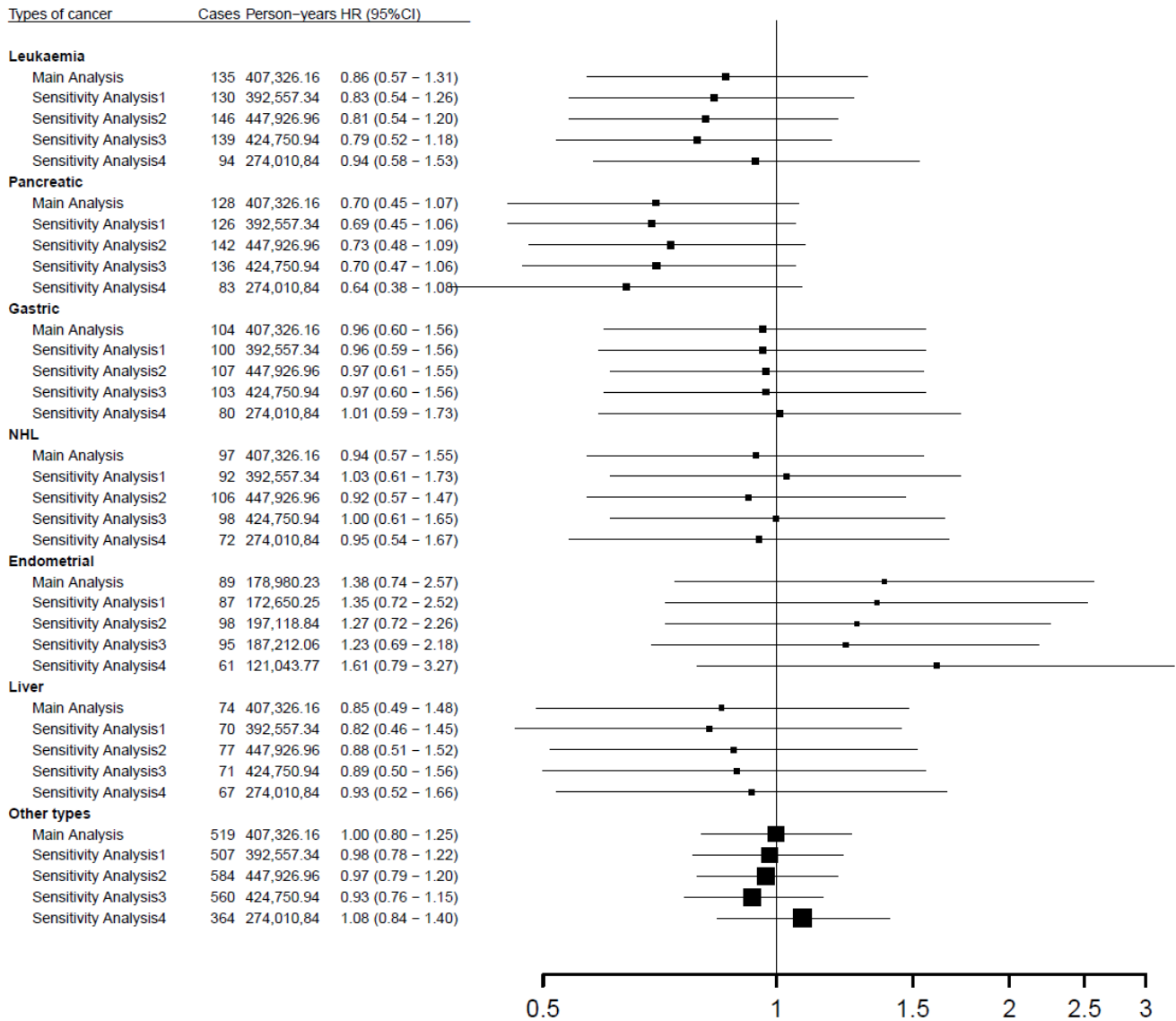
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**Supplementary Figure 3.** Multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) for the association between initiators of metformin monotherapy and initiators of sulfonylurea monotherapy and risk of colorectal, prostate, lung, postmenopausal breast, bladder, esophageal cancer and melanoma using the intention-to-treat principle in the CPRD by type of sensitivity analyses. (Sensitivity analysis 1: after excluding participants with any treatment breaks of more than 90 days during the initial qualifying twelve-month exposure period. Sensitivity analysis 2: the exposure to an antidiabetic drug class was redefined based on the first six months of each participant's prescription record compared to the twelve-month treatment period used in the primary analysis. Sensitivity analysis 3: after excluding participants with any treatment breaks of more than 90 days during the latter qualifying six-month exposure period. Sensitivity analysis 4: after excluding the initial 36 months of follow-up after the first antidiabetic prescription).



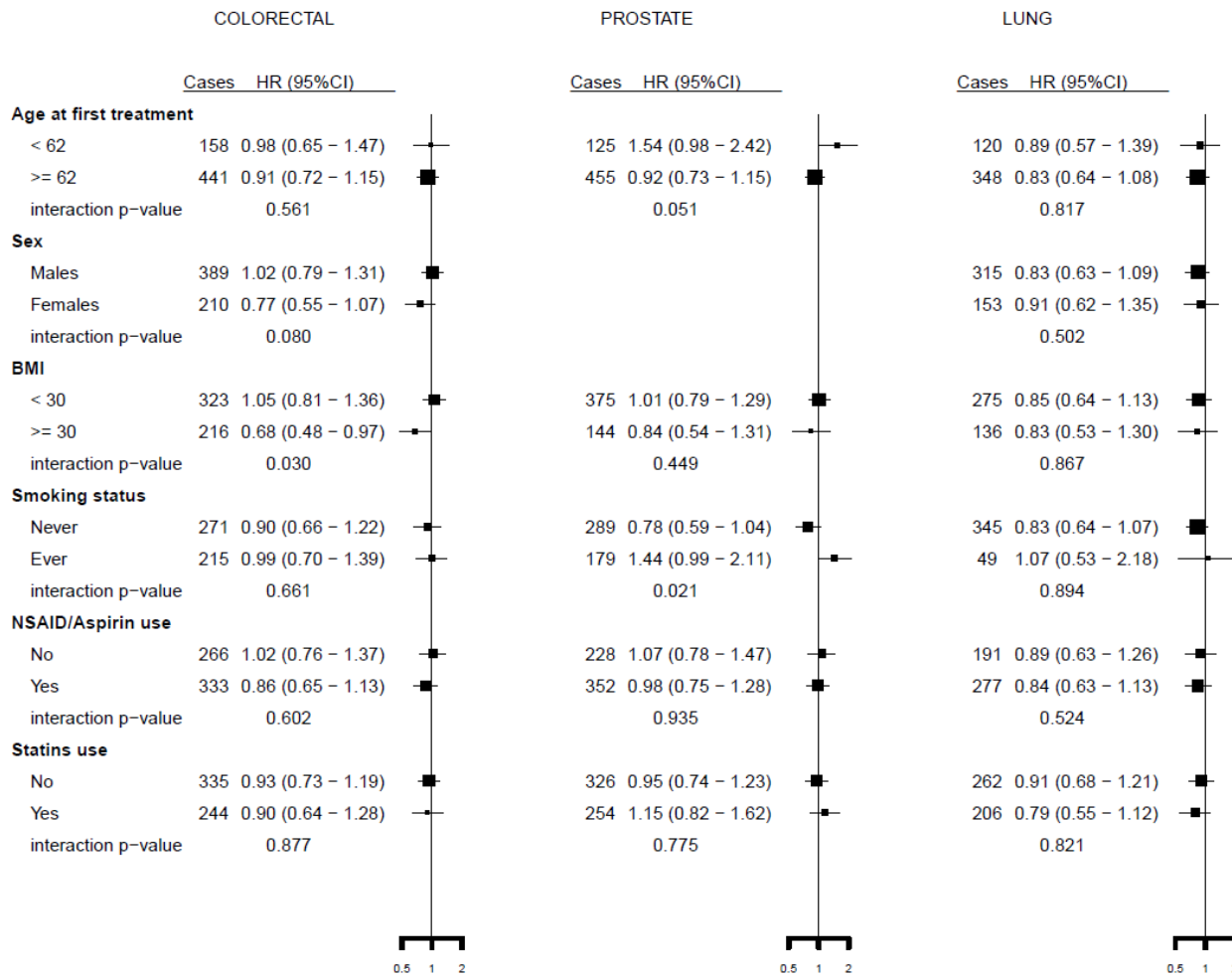
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**Supplementary Figure 4.** Multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) for the association between initiators of metformin monotherapy and initiators of sulfonylurea monotherapy and risk of leukemia, non-Hodgkin's lymphoma, and pancreatic, gastric, endometrial, liver and other types of cancer using the intention-to-treat principle in the CPRD by type of sensitivity analyses. (Sensitivity analysis 1: after excluding participants with any treatment breaks of more than 90 days during the initial qualifying twelve-month exposure period. Sensitivity analysis 2: the exposure to an antidiabetic drug class was redefined based on the first six months of each participant's prescription record compared to the twelve-month treatment period used in the primary analysis. Sensitivity analysis 3: after excluding participants with any treatment breaks of more than 90 days during the latter qualifying six-month exposure period. Sensitivity analysis 4: after excluding the initial 36 months of follow-up after the first antidiabetic prescription).



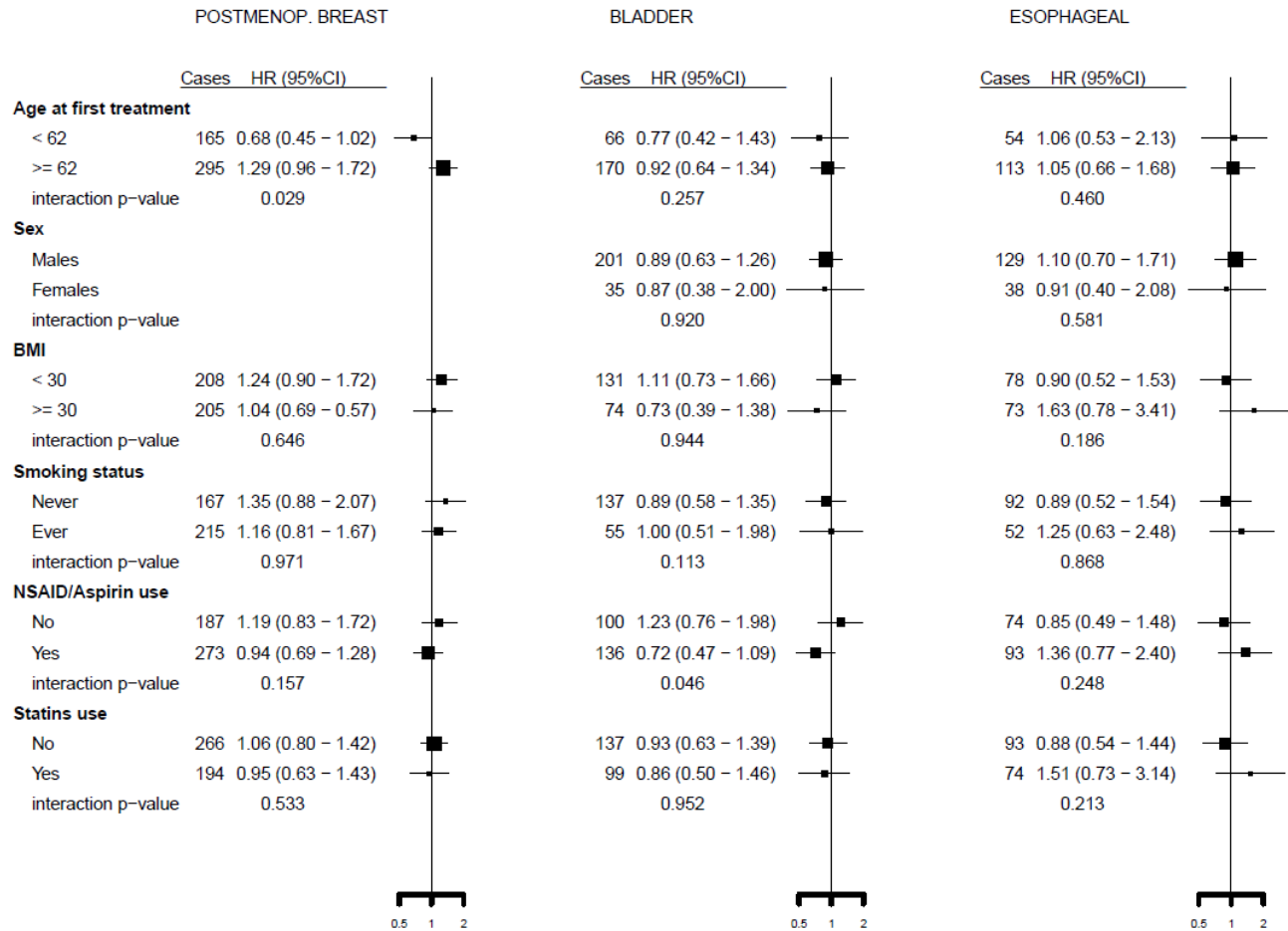
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**Supplementary Figure 5.** Multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) for the association between initiators of metformin monotherapy and initiators of sulfonylurea monotherapy and risk of colorectal, prostate and lung cancer using the intention-to-treat principle in the CPRD by subgroups.



SUPPLEMENTARY DATA

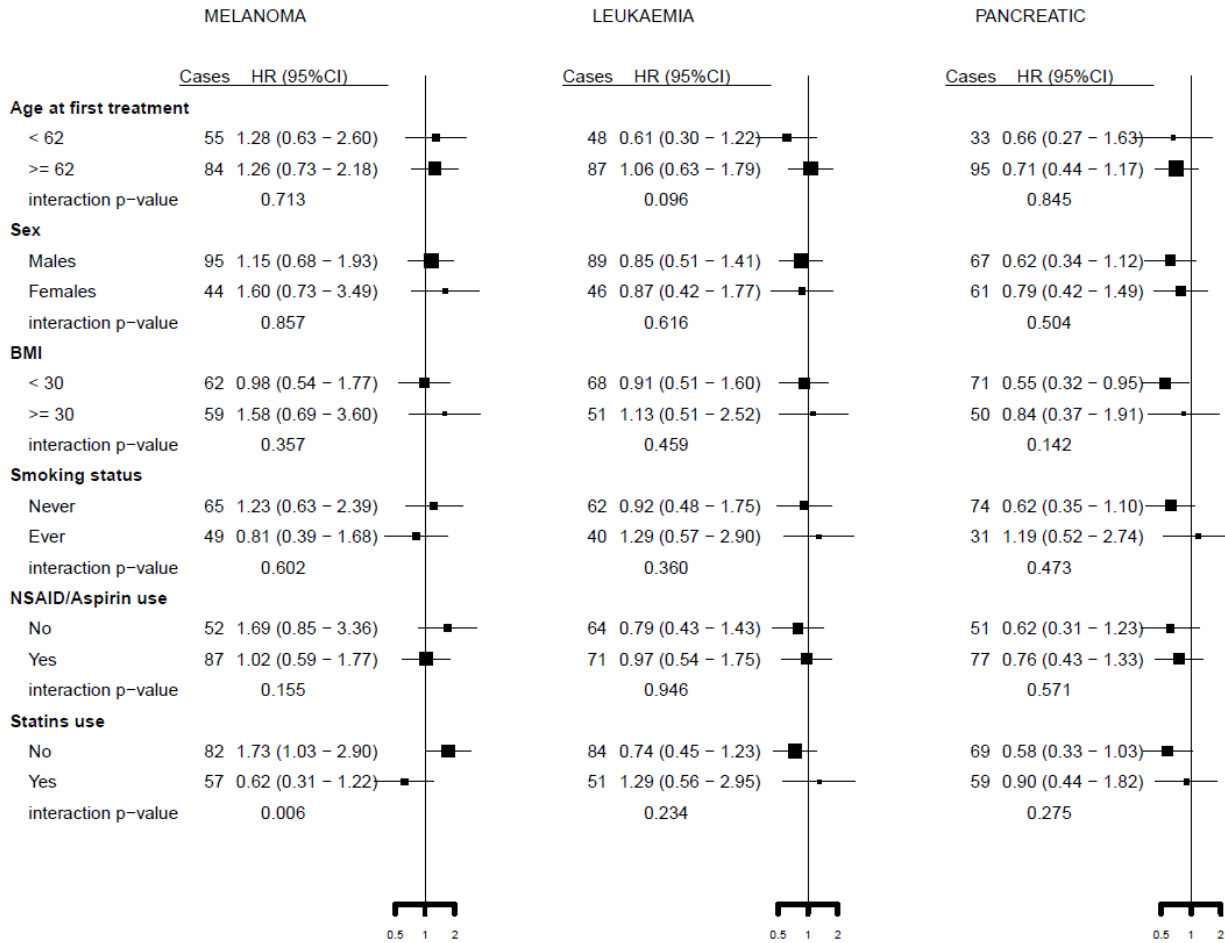
**Supplementary Figure 6.** Multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) for the association between initiators of metformin monotherapy and initiators of sulfonylurea monotherapy and risk of postmenopausal breast, bladder and esophageal cancer using the intention-to-treat principle in the CPRD by subgroups.





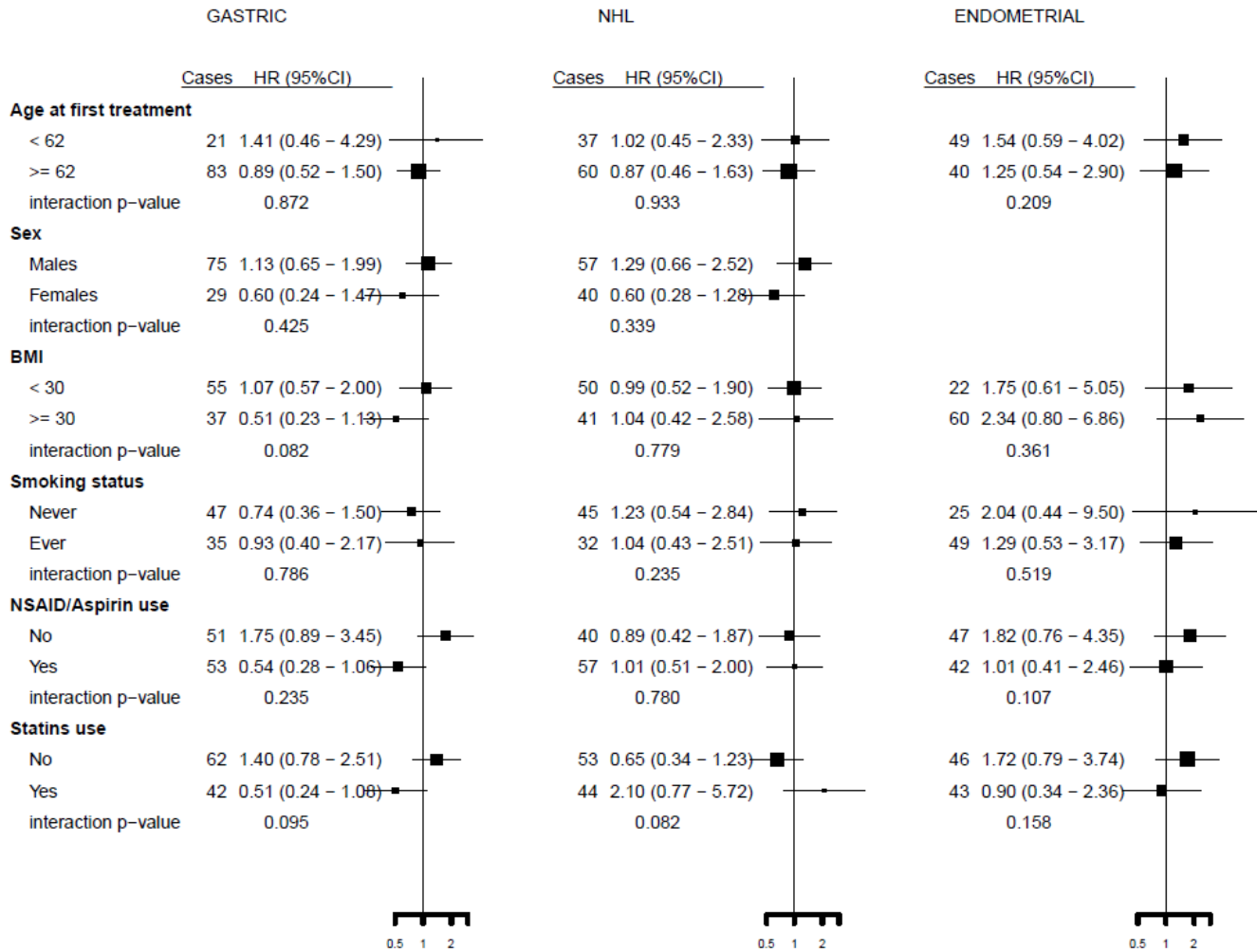
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**Supplementary Figure 7.** Multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) for the association between initiators of metformin monotherapy and initiators of sulfonylurea monotherapy and risk of melanoma, leukemia and pancreatic cancer using the intention-to-treat principle in the CPRD by subgroups.



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**Supplementary Figure 8.** Multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) for the association between initiators of metformin monotherapy and initiators of sulfonylurea monotherapy and risk of non-Hodgkin's lymphoma, gastric and endometrial cancer using the intention-to-treat principle in the CPRD by subgroups.



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**Supplementary Figure 9.** Multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) for the association between initiators of metformin monotherapy and initiators of sulfonylurea monotherapy and risk of liver and other types of cancer using the intention-to-treat principle in the CPRD by subgroups.

