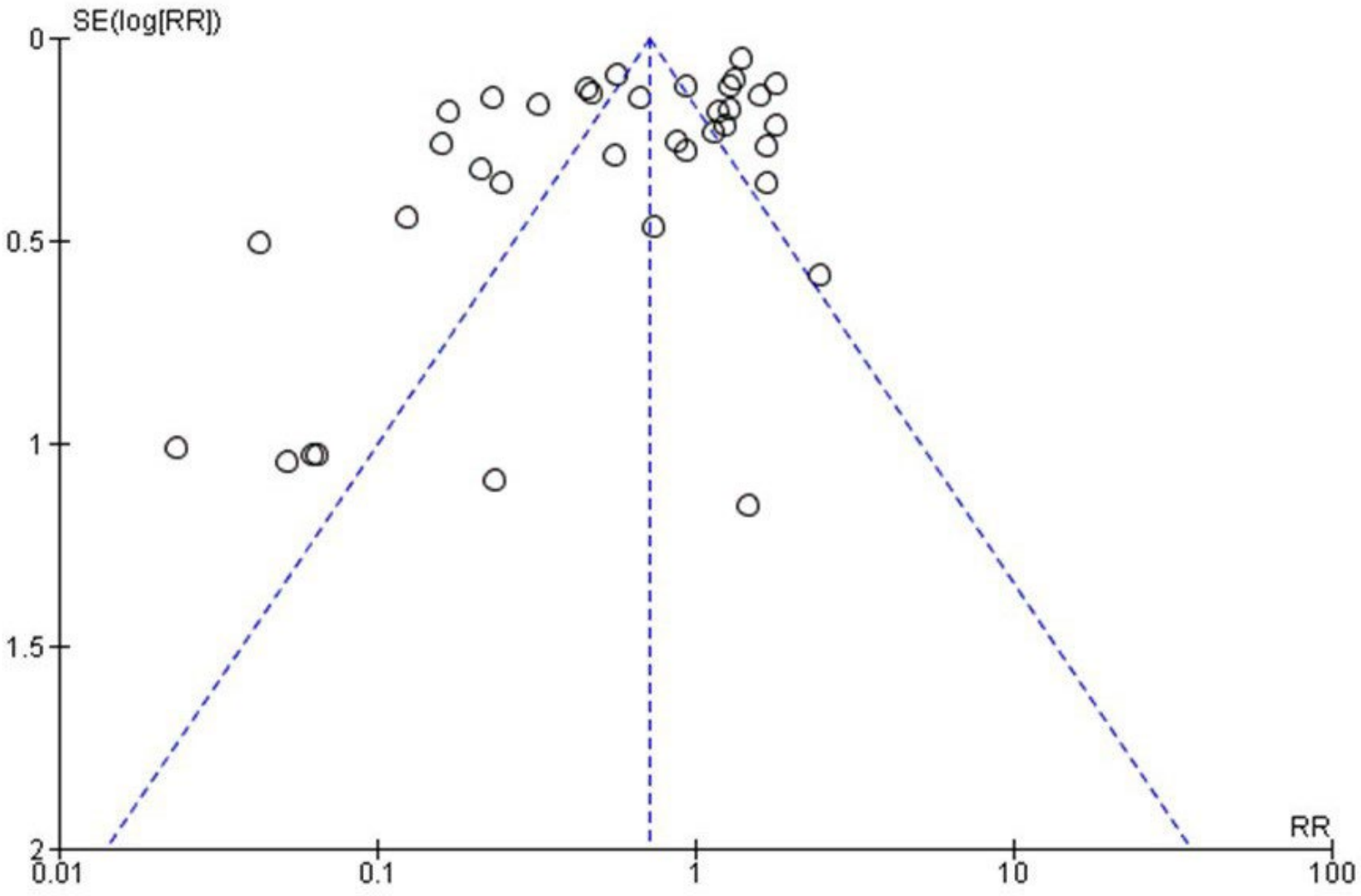
Supplemental Online Content

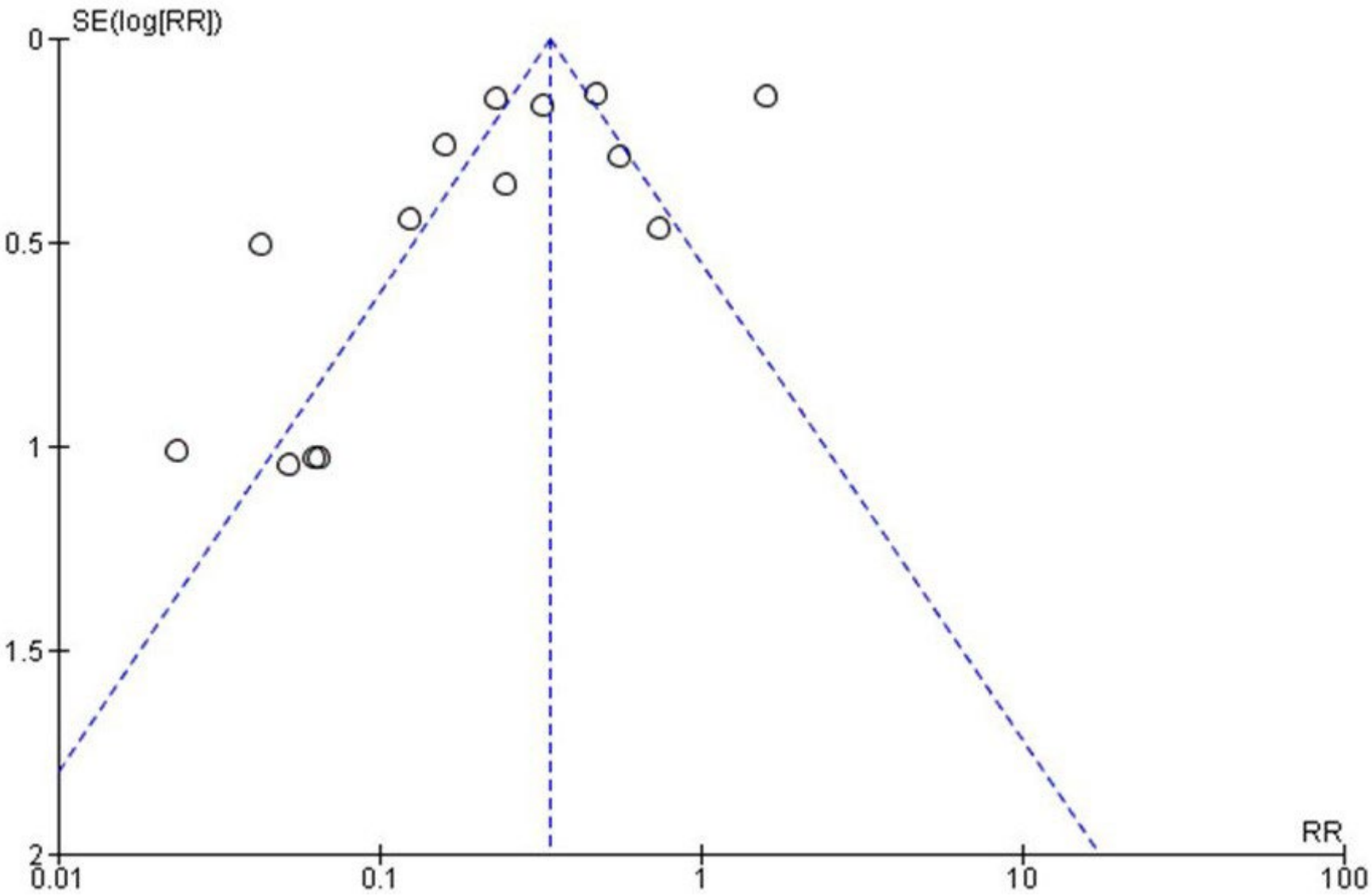
Farooq MZ, Aqeel SB, Lingamaneni P, et al. Association of immune checkpoint inhibitors with neurologic adverse events: a systematic review and meta-analysis. *JAMA Netw Open.* 2022;5(4):e227722. doi:10.1001/jamanetworkopen.2022.7722

This supplemental material has been provided by the authors to give readers additional information about their work.

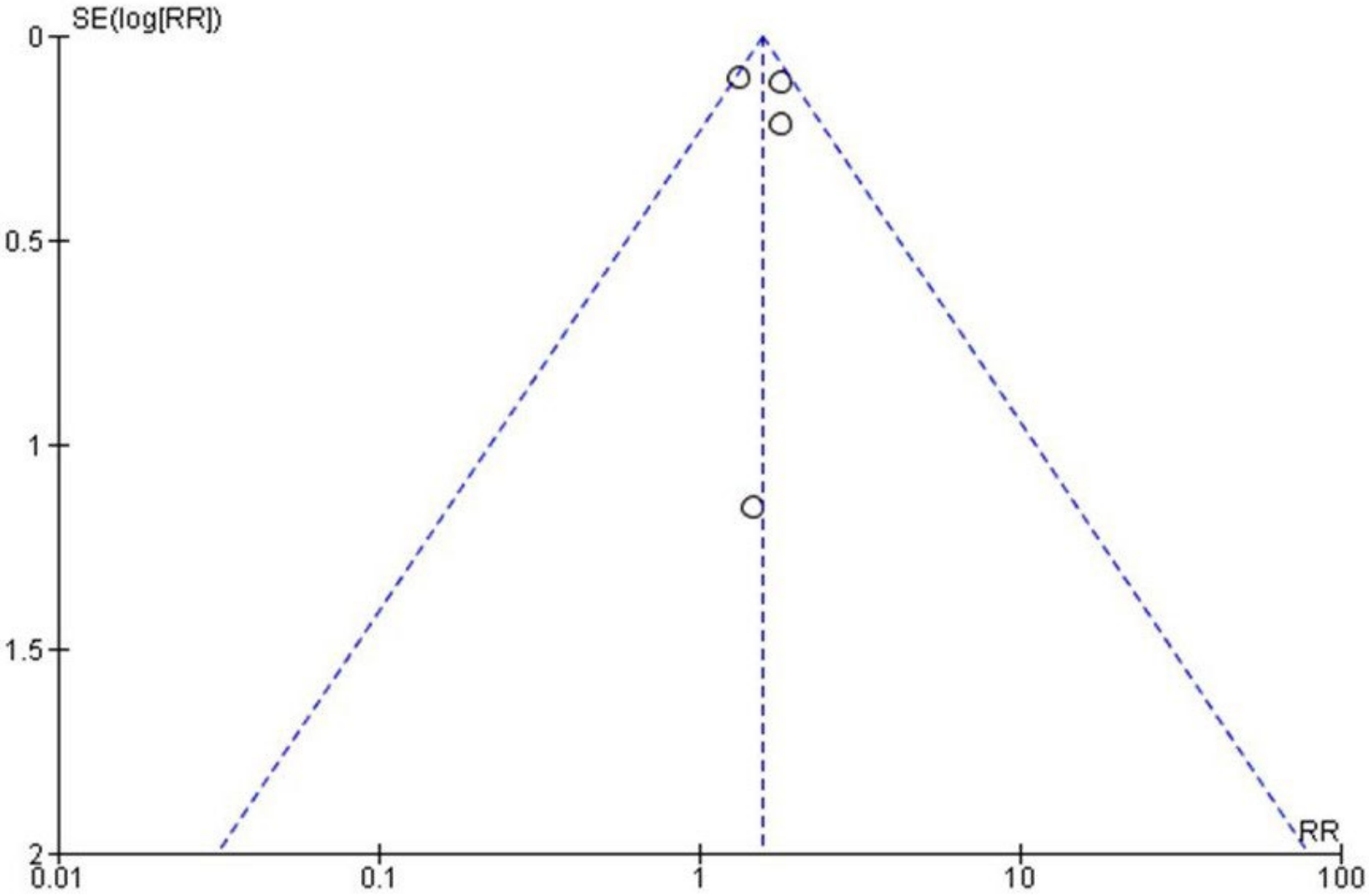
eFigure 1. Funnel Plots for Included Trials by Subgroup



A. Funnel plots for trials included in overall analysis.

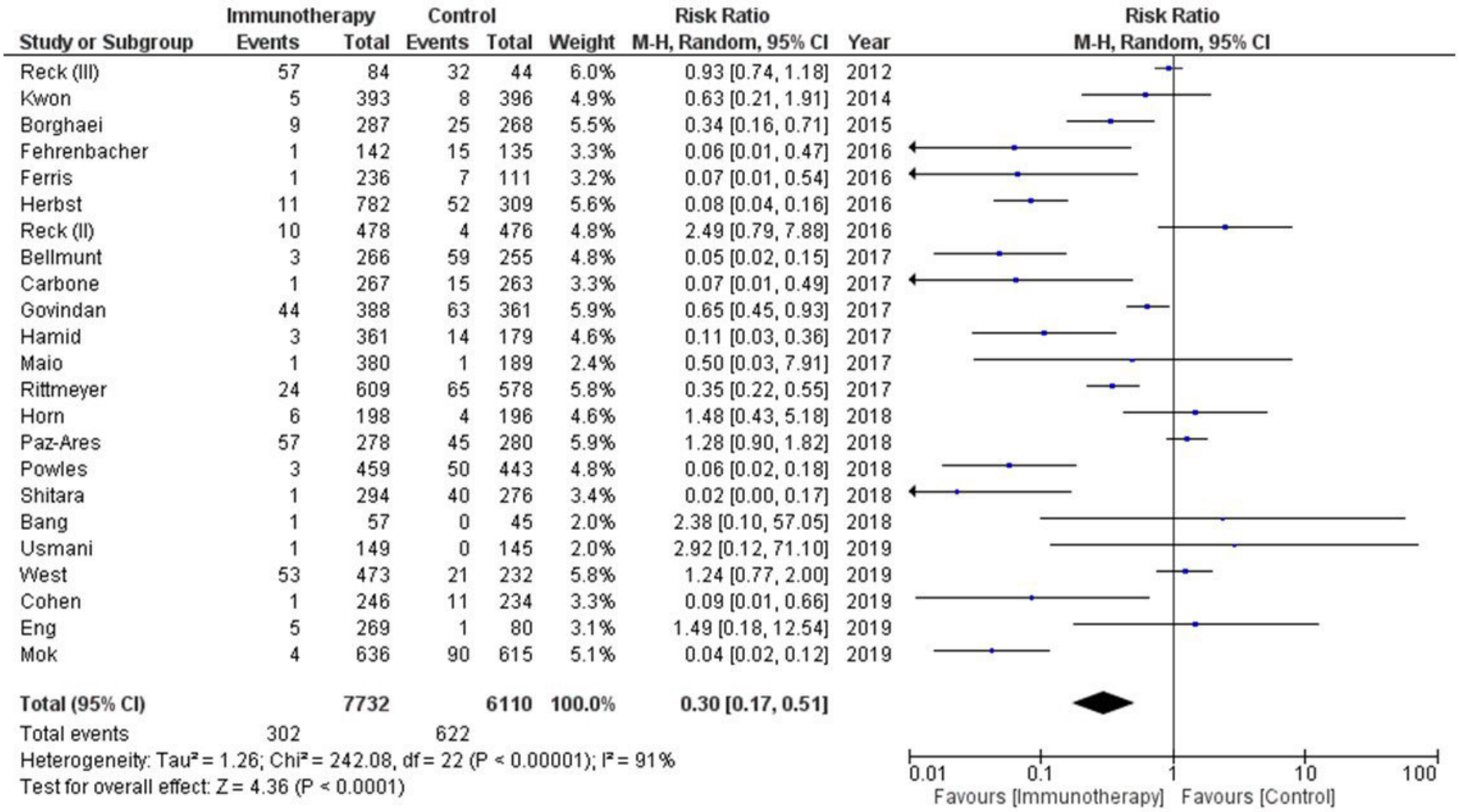


B. Funnel plots for trials included in the subgroup analysis of immunotherapy versus chemotherapy.

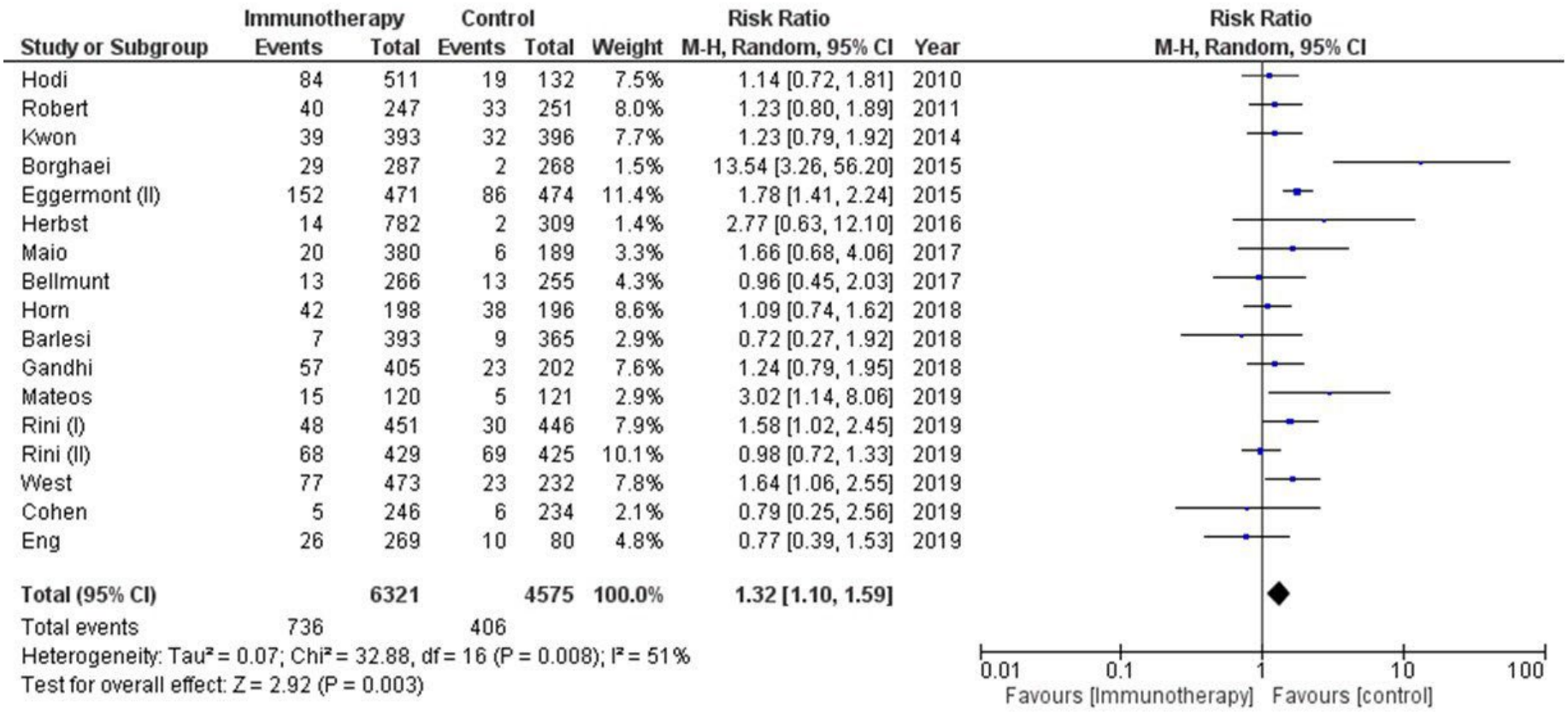


C. Funnel plots for trials included in the subgroup analysis of immunotherapy versus placebo

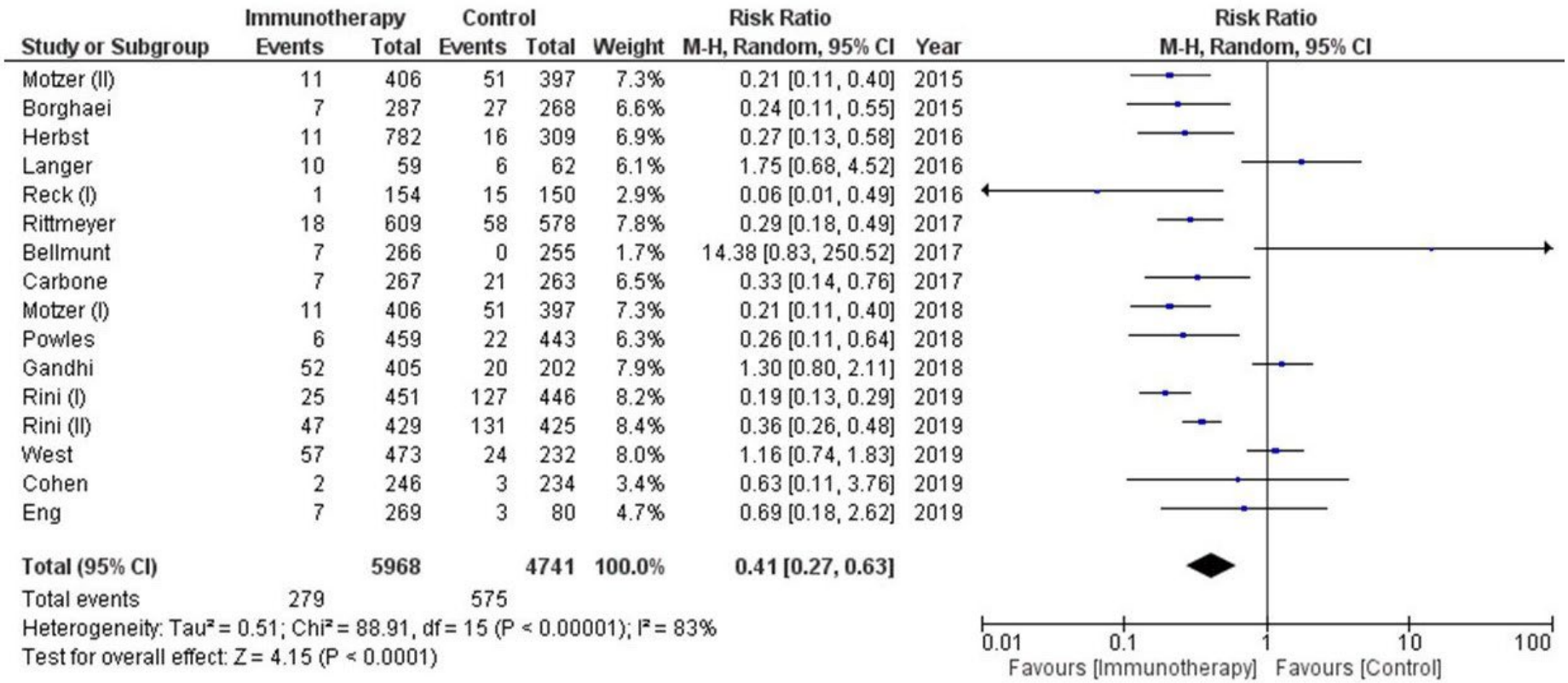
eFigure 2. Overall Analysis of Incidence of Adverse Events Between Checkpoint Inhibitor and Control Arm



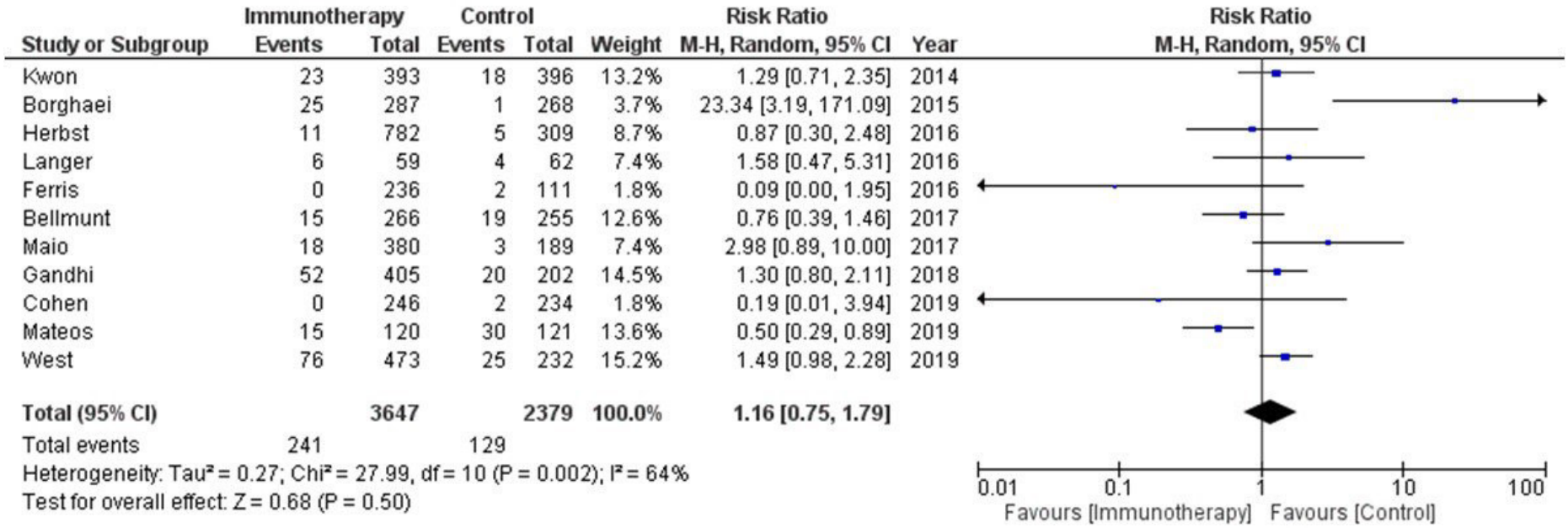
A. Peripheral neuropathy



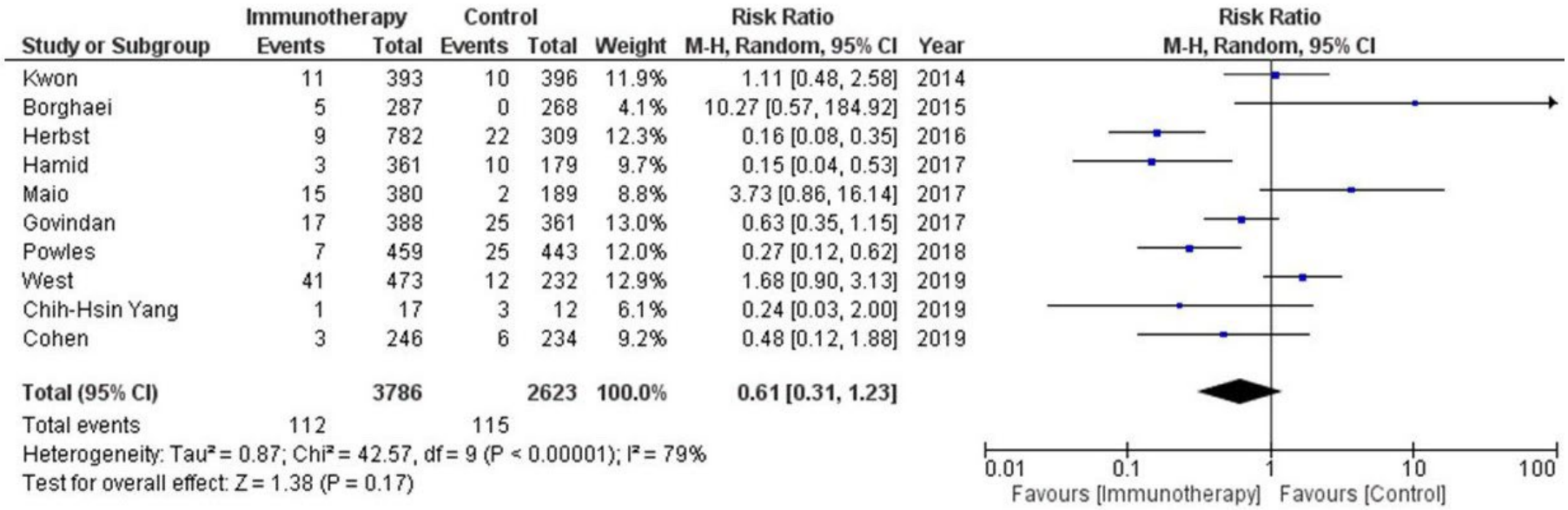
B. Headache



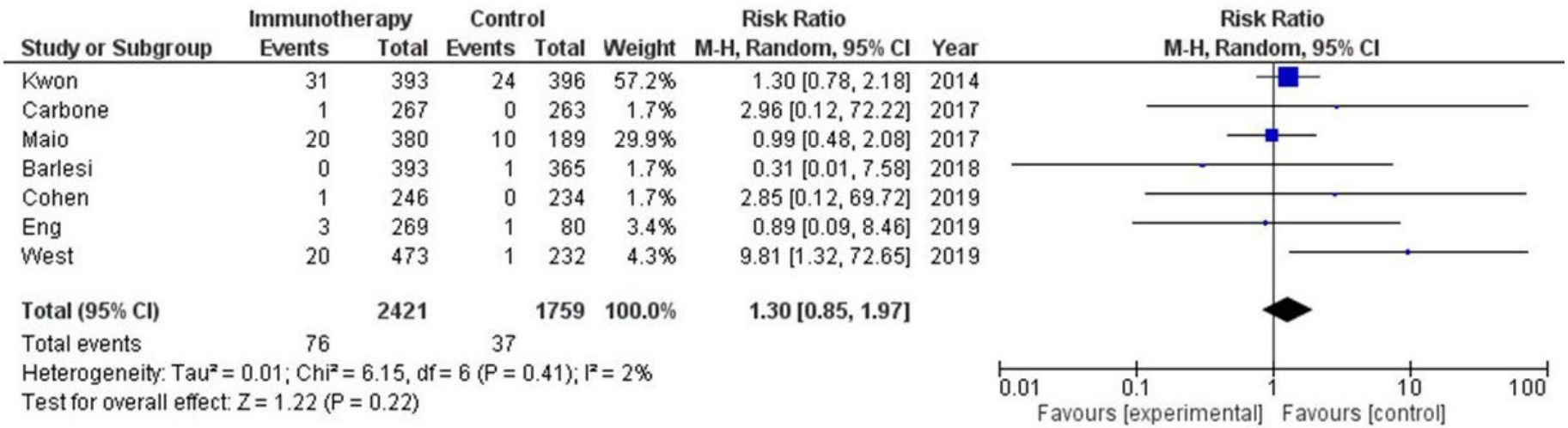
C. Dysgeusia



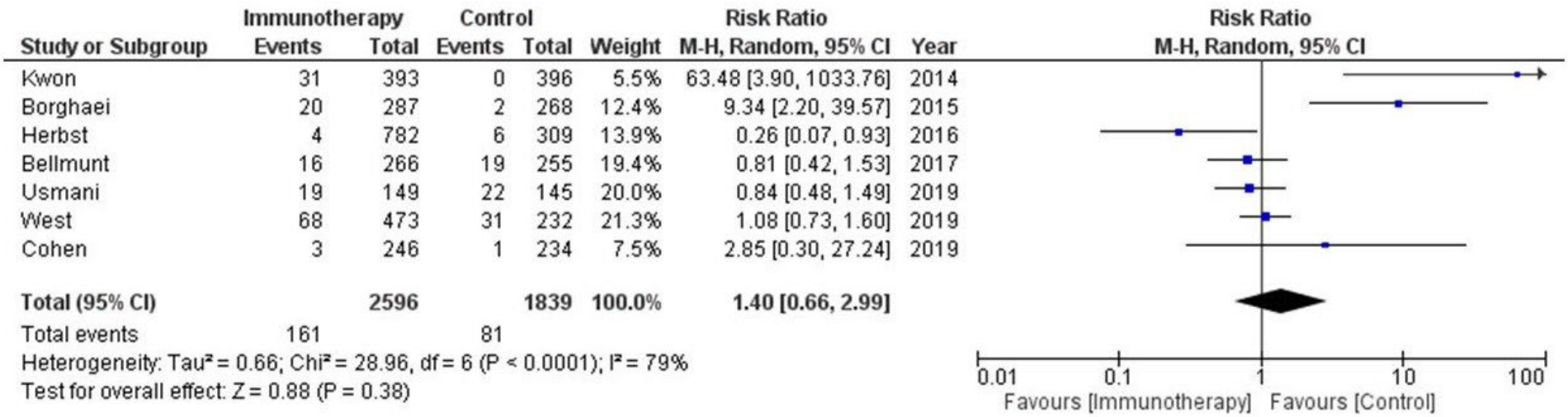
D. Dizziness



E. Paresthesia

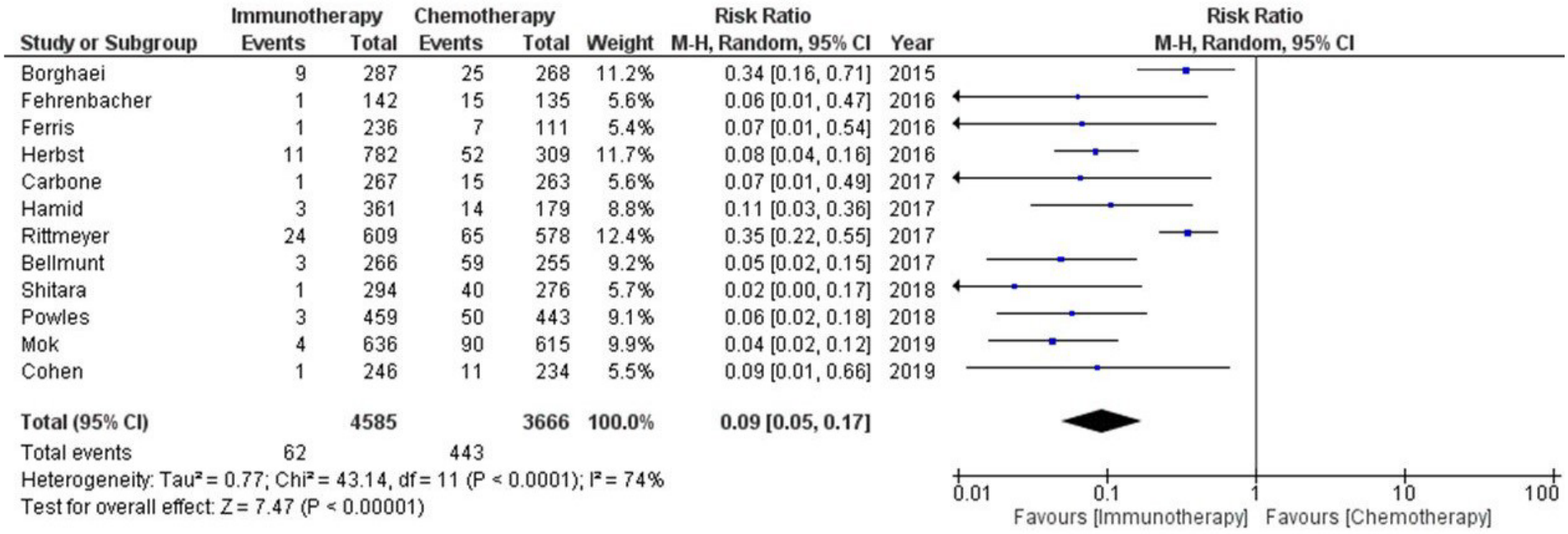


F. Altered mental status

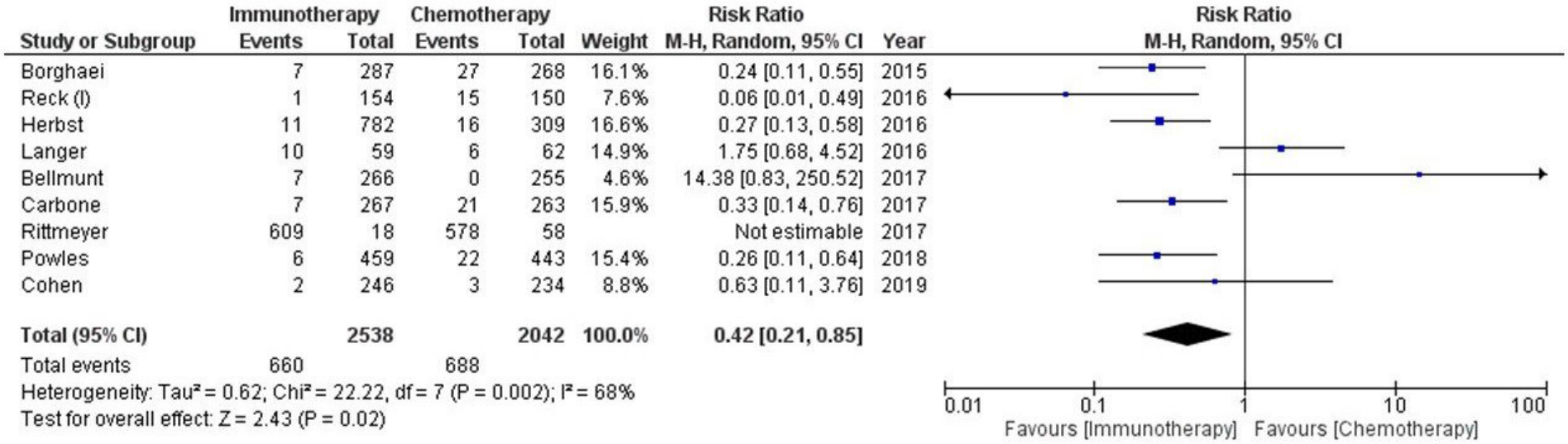


G. Insomnia

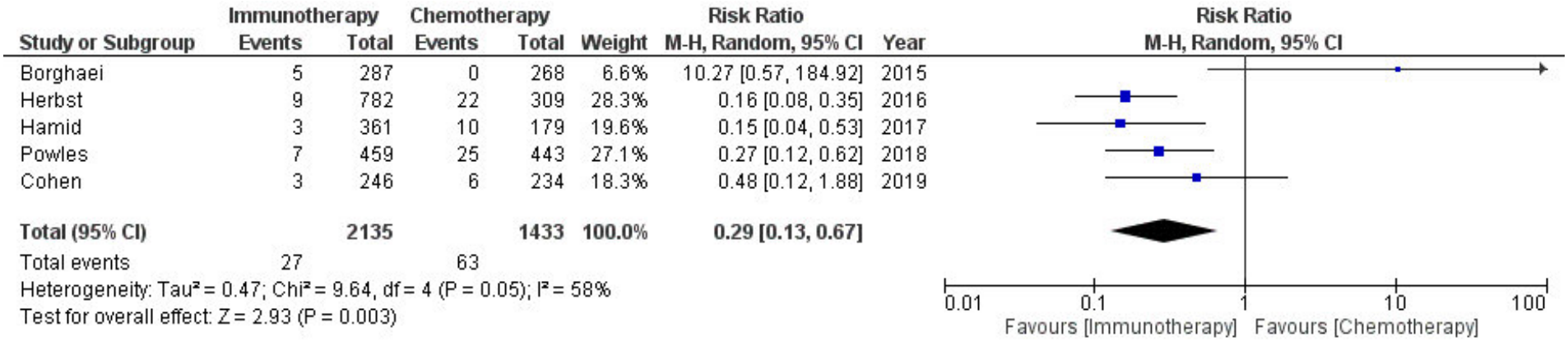
eFigure 3. Subgroup Analysis of Adverse Events Between Checkpoint Inhibitors and Chemotherapy



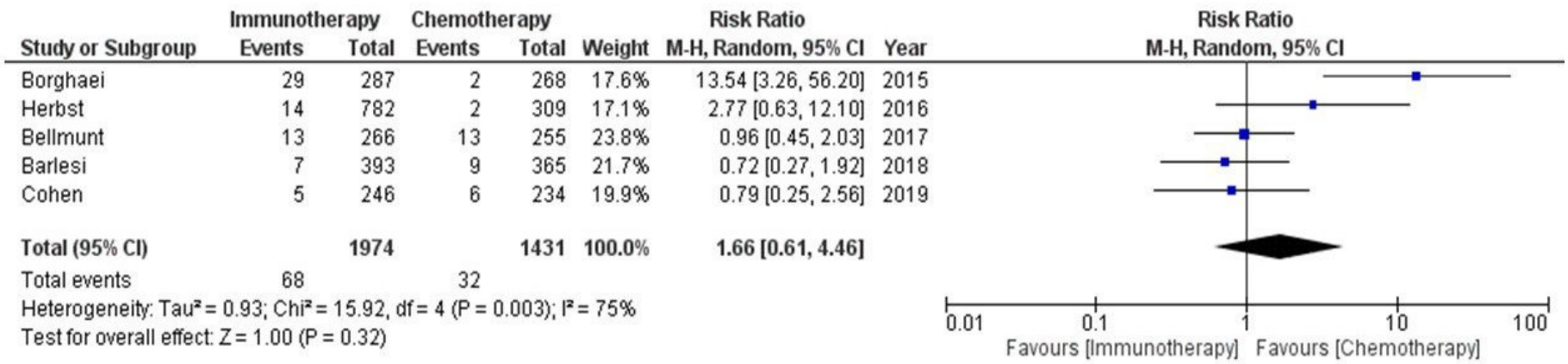
A. Peripheral neuropathy



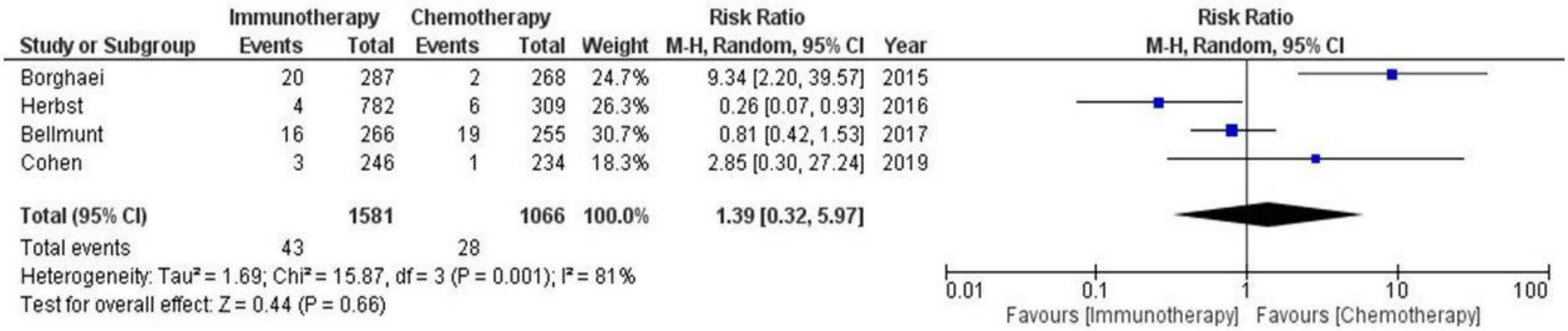
B. Dysgeusia



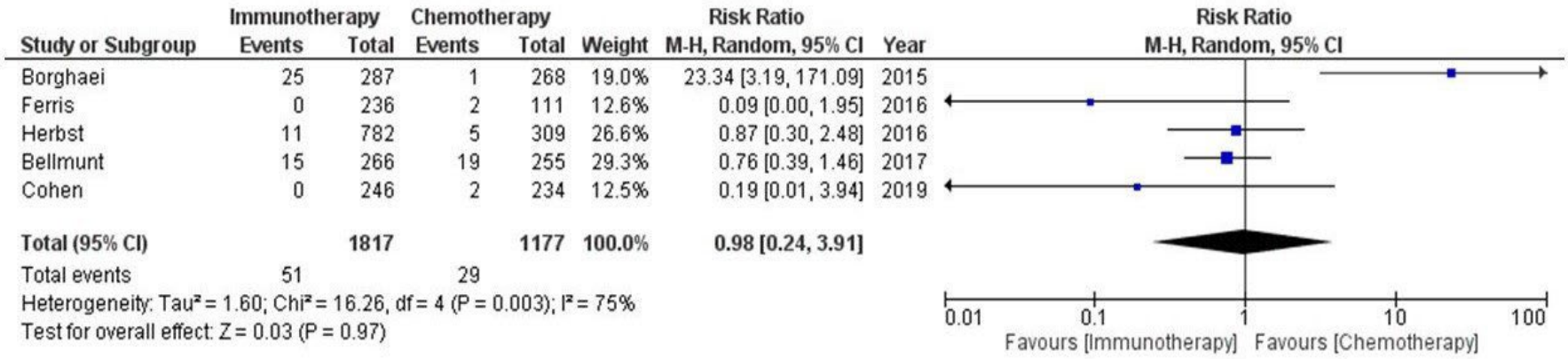
C. Paresthesia



D. Headache

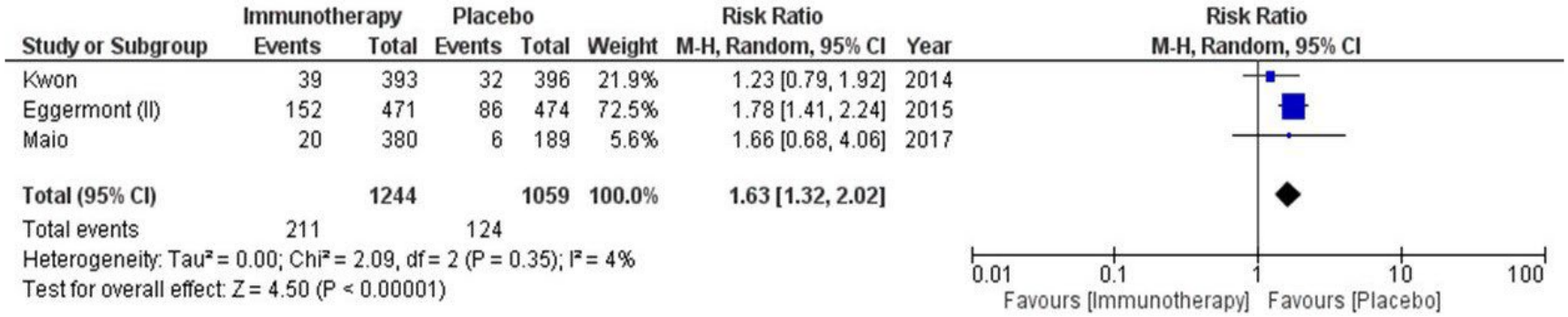


E. Insomnia

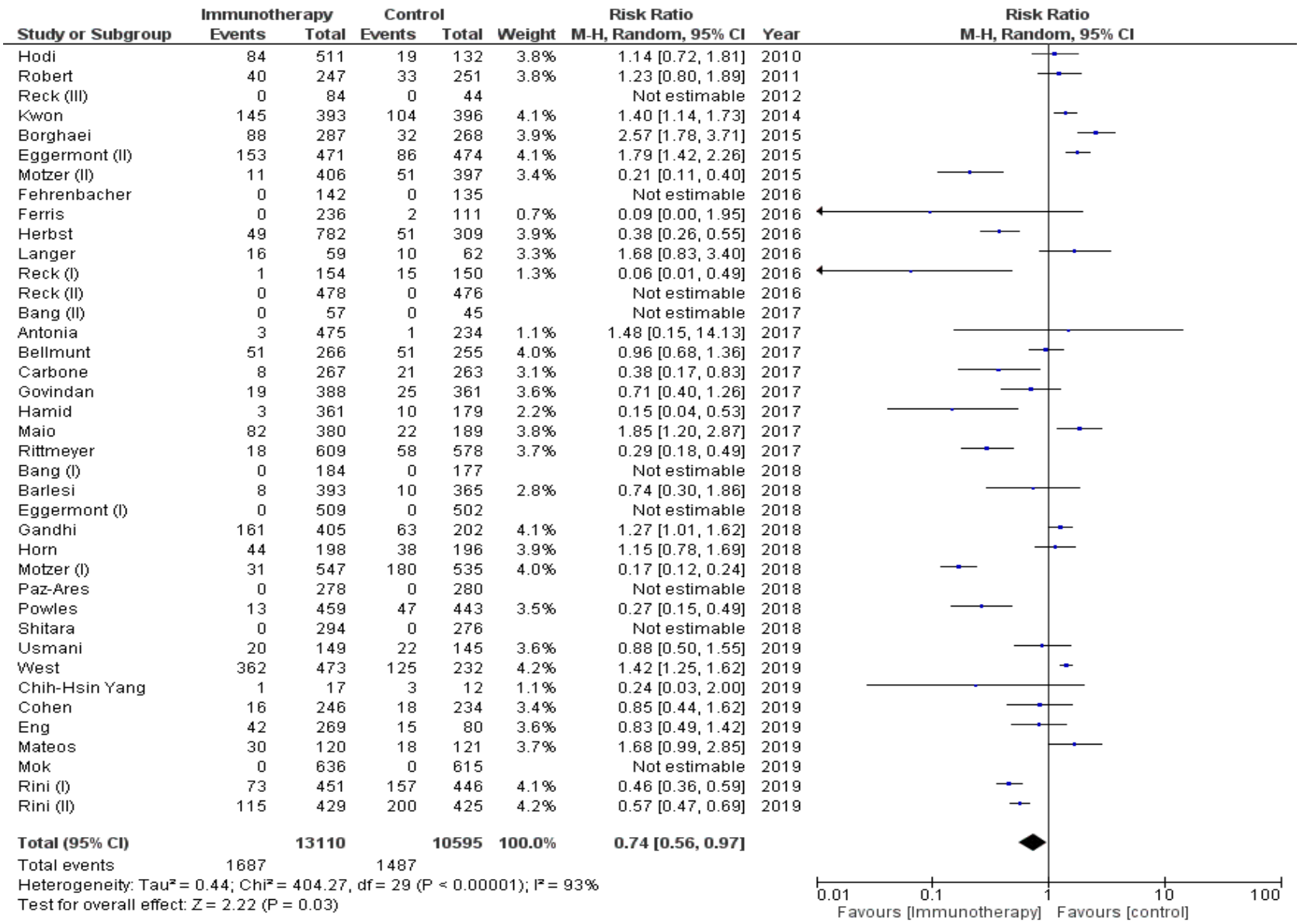


F. Dizziness

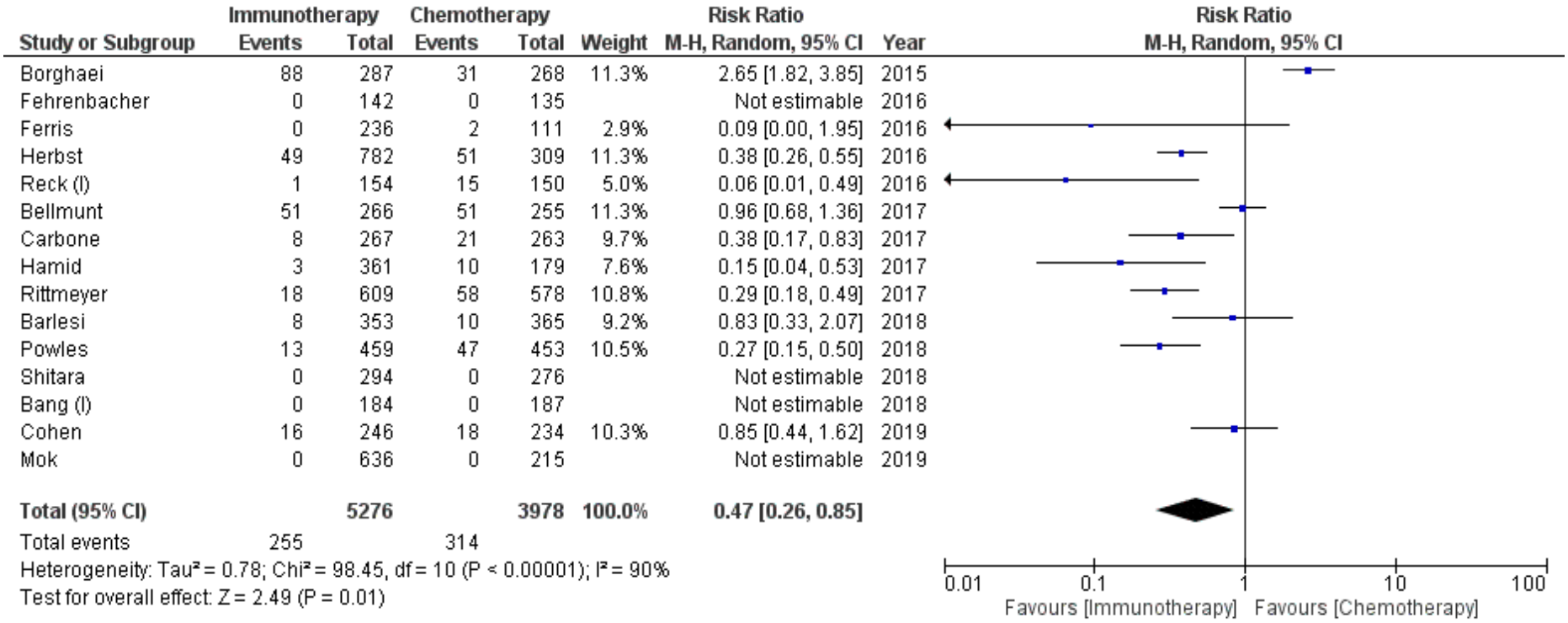
eFigure 4. Subgroup Analysis of Headache Between Checkpoint Inhibitors and Placebo



eFigure 5. Overall Risk of Neurologic Adverse Events Excluding Incidence of Specific Event Between Checkpoint Inhibitors and Control Arm



A. Excluding the Incidence of Peripheral Neuropathy



B. Excluding the Incidence of Peripheral Neuropathy

eTable 1. Quality Assessment of All Trials Using the Cochrane Collaborations Tool

Article	Selection Bias		Performance Bias	Detection bias	Attrition bias	Reporting Bias	Other bias	Our evaluation
	Random Sequence Generation	**Allocation concealment**	**Blinding of participants and personnel**	**Blinding of outcome assessment**	**Incomplete outcome data**	**Selective Reporting**	**Anything else, ideally prespecified**	
Chih-Hsin Yang	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Cohen	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Eng	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Mateos	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Mok	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Rini (1)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Rini (2)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Usmani	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
West	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Bang (1)	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Fair quality
Barlesi	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Eggermont	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Gandhi	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Horn	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Motzer	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Paz-Ares	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Powles	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Shitara	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Antonia	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Bang (2)	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Fair quality
Bellmunt	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Carbone	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Fair quality
Govindan	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Fair quality
Hamid	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Maio	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Rittmeyer	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Fehrenbacher	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Ferris	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Herbst	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Langer	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Reck (I)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Reck (II)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Borghaei	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality

Eggermont (II)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Article	Selection Bias		Performance Bias		Detection bias		Other bias	Our evaluation
	Random Sequence Generation	**Allocation concealment**	**Blinding of participants and personnel**	**Blinding of outcome assessment**	**Incomplete outcome data**	**Selective Reporting**	**Anything else, ideally prespecified**	
Motzer (II)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Kwon	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Reck	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Fair quality
Robert	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Hodi	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality

eTable 2. Pooled Characteristics of the Intention-to-Treat Population

Variable	**Control group (All drug regimens in the comparison arm)** N=10775	**Immune checkpoint inhibitor group** N=12958
Age	Unable to estimate	Unable to estimate
Female sex — no. (%)	3315 (30.8)	4283 (33.1)
Race — no. (%)		
White	3365 (31.2)	4501 (34.7)
African American/black	56 (0.1)	91 (0.1)
Asian	779 (7.2)	924 (7.1)
Other	50 (<0.1)	74 (0.1)
Unknown/not reported	6525 (60.1)	7368 (56.9)
Region		
North America	496 (4.6)	664 (5.1)
Europe	1353 (12.6)	1522 (11.8)
Asia	715 (6.6)	804 (6.2)
Latin America	192 (1.8)	205 (1.6)
Unspecified/not reported	8019 (74.4)	9763 (75.3)
Tumor type		
Non-small cell lung cancer	4060 (37.6)	5116 (39.5)
Renal cell carcinoma	1847 (17.1)	1846 (14.2)
Malignant melanoma	1548 (14.4)	2140 (16.5)
Small cell lung cancer	723 (6.7)	764 (5.9)
Urothelial	736 (6.8)	737 (5.7)
Gastric/gastroesophageal junction cancer	539 (5.0)	538 (4.2)
HNSCC	369 (3.4)	487 (3.8)
Prostate	400 (3.7)	399 (3.1)
Tumor Type (continued)		
Multiple myeloma	274 (2.5)	276 (2.1)
Malignant mesothelioma	189 (1.8)	382 (2.9)
Colorectal cancer	90 (0.1)	273 (2.1)
ECOG performance-status score — no. (%)		
0	2890 (26.8)	3725 (28.7)
1	4757 (44.1)	5855 (45.2)
2	23 (0.2)	22 (0.2)
Unknown/not reported/used Karnofsky performance status	3105 (28.8)	3356 (25.9)
Smoking status — no. (%)		
Current or former smoker	4132 (38.3)	5105 (39.4)
Never smoker	895 (8.3)	1109 (8.6)
Unknown/not reported	5748 (53.3)	6744 (52.0)

ECOG- Eastern Cooperative Oncology Group; HNSCC- Head and Neck Squamous Cell Carcinoma.