Additional file 2

Comparison of HPV vaccine study documents: meta-analyses

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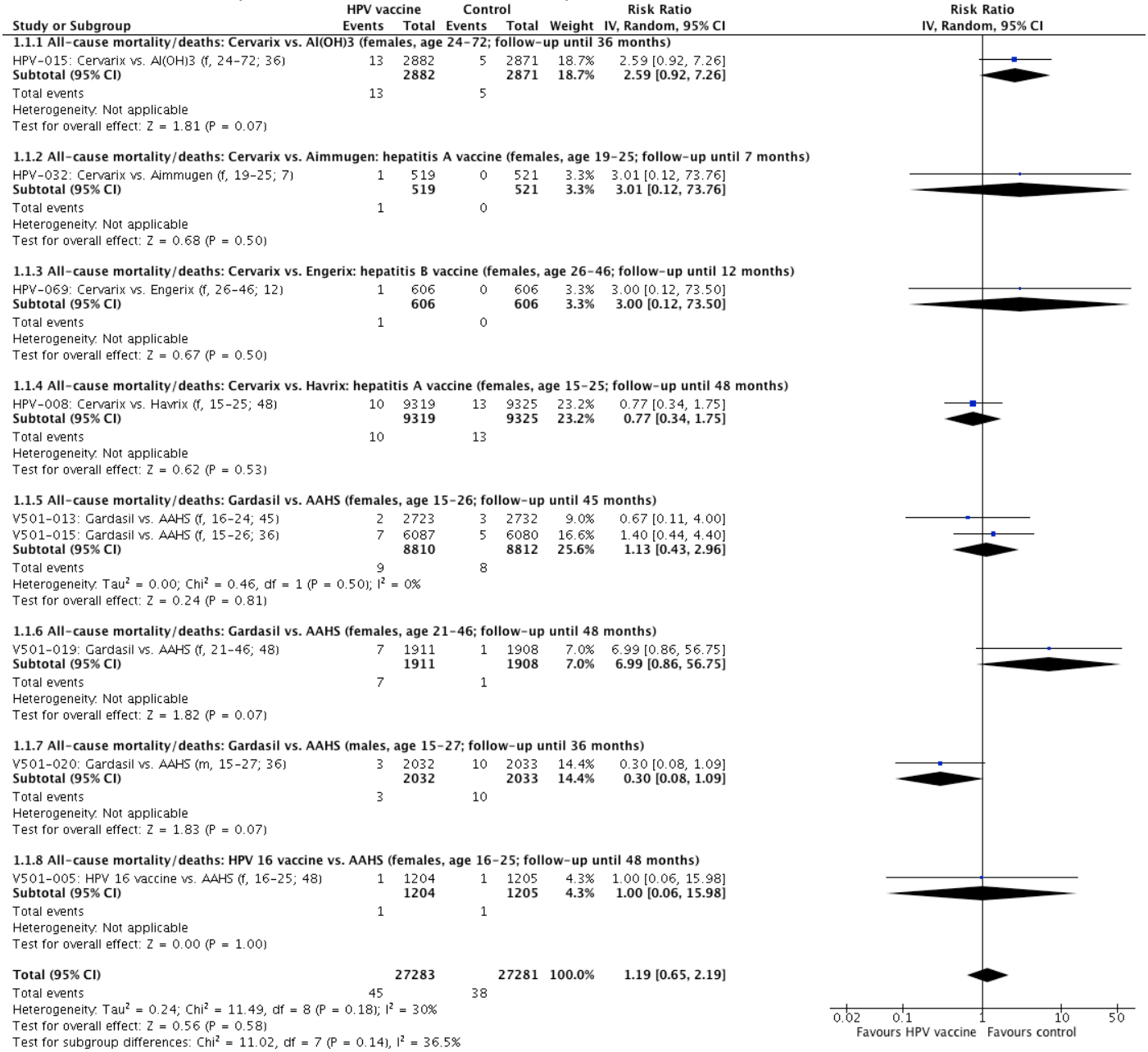
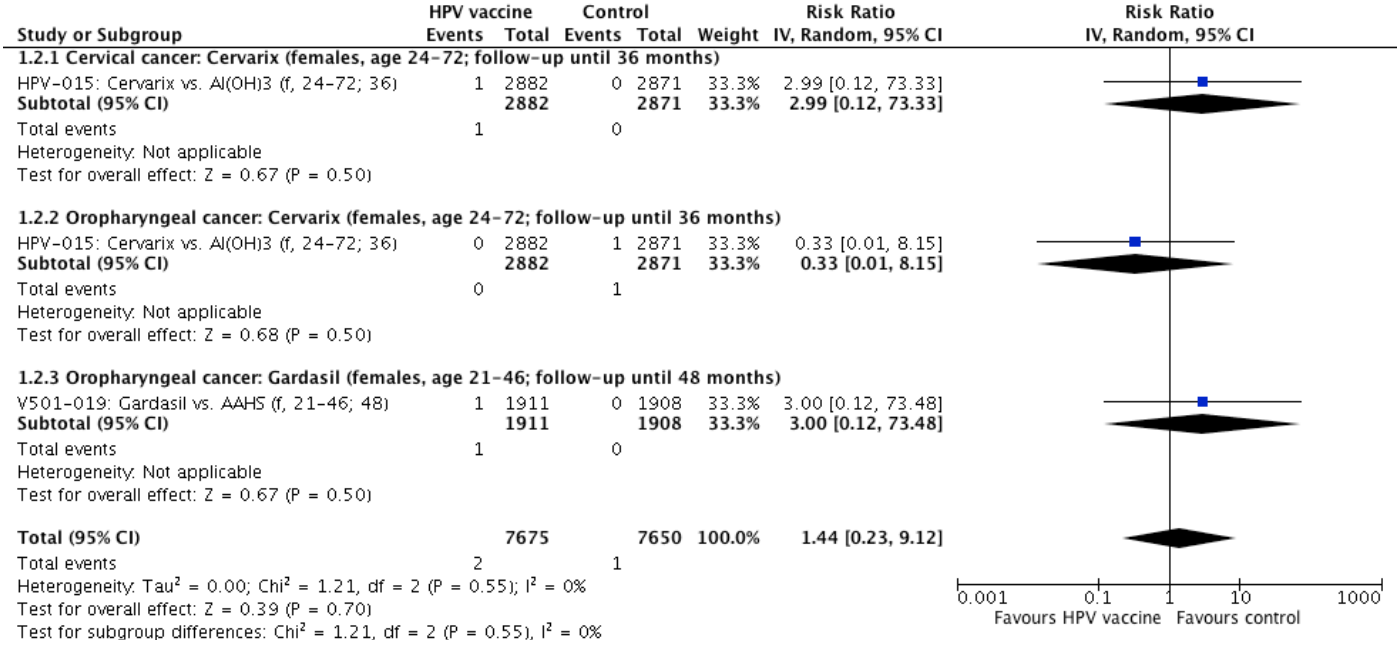
1. Clinical study reports

1.1. All-cause mortality/deaths*: intention to treat analysis



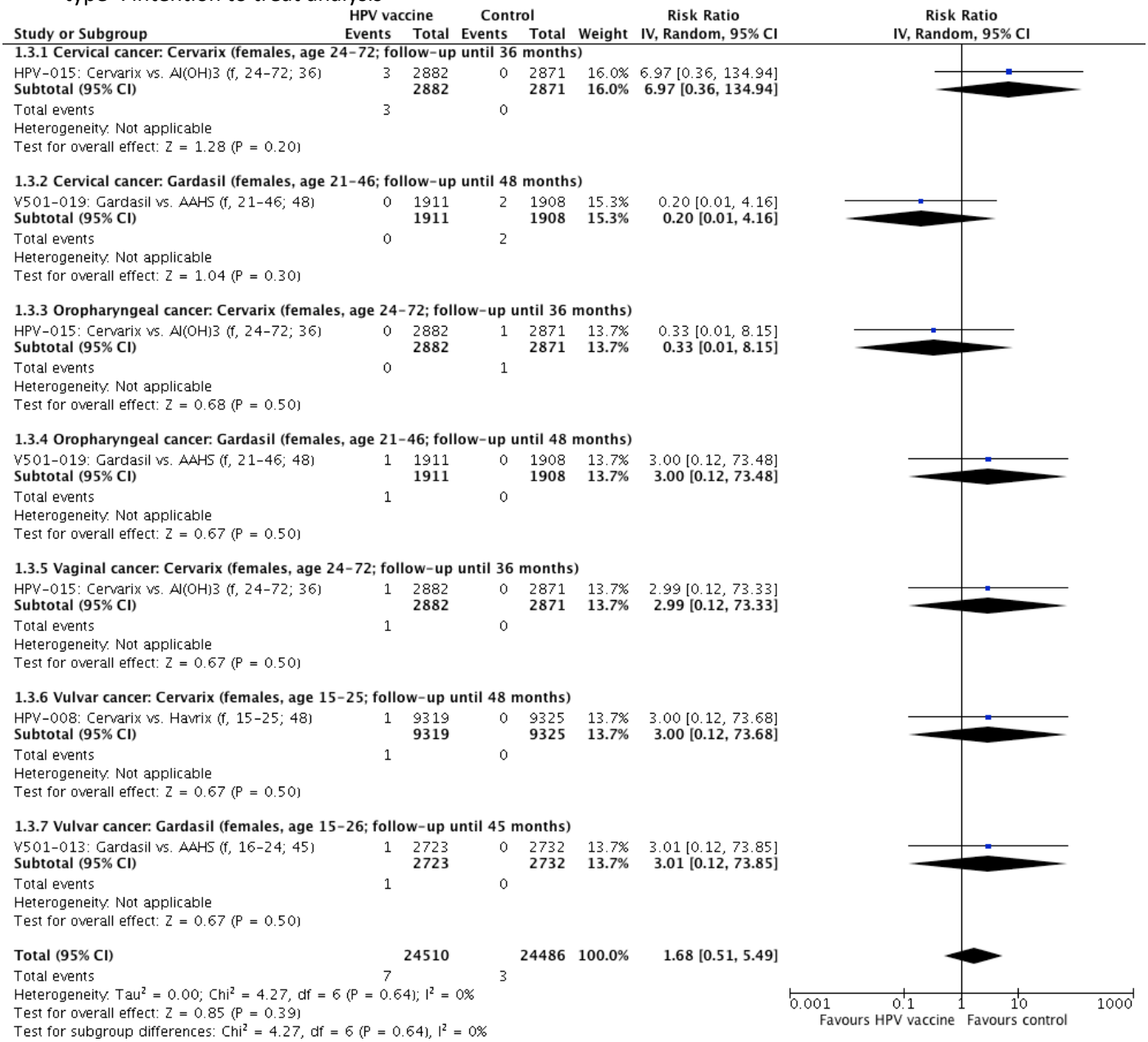
*1.1. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 1.43 [0.65, 3.15]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 1.08 [0.40, 2.96].

1.2. Mortality/deaths from HPV-related cancers (anal, cervical, oropharyngeal, penile, vaginal and vulvar) irrespective of HPV type*: intention to treat analysis



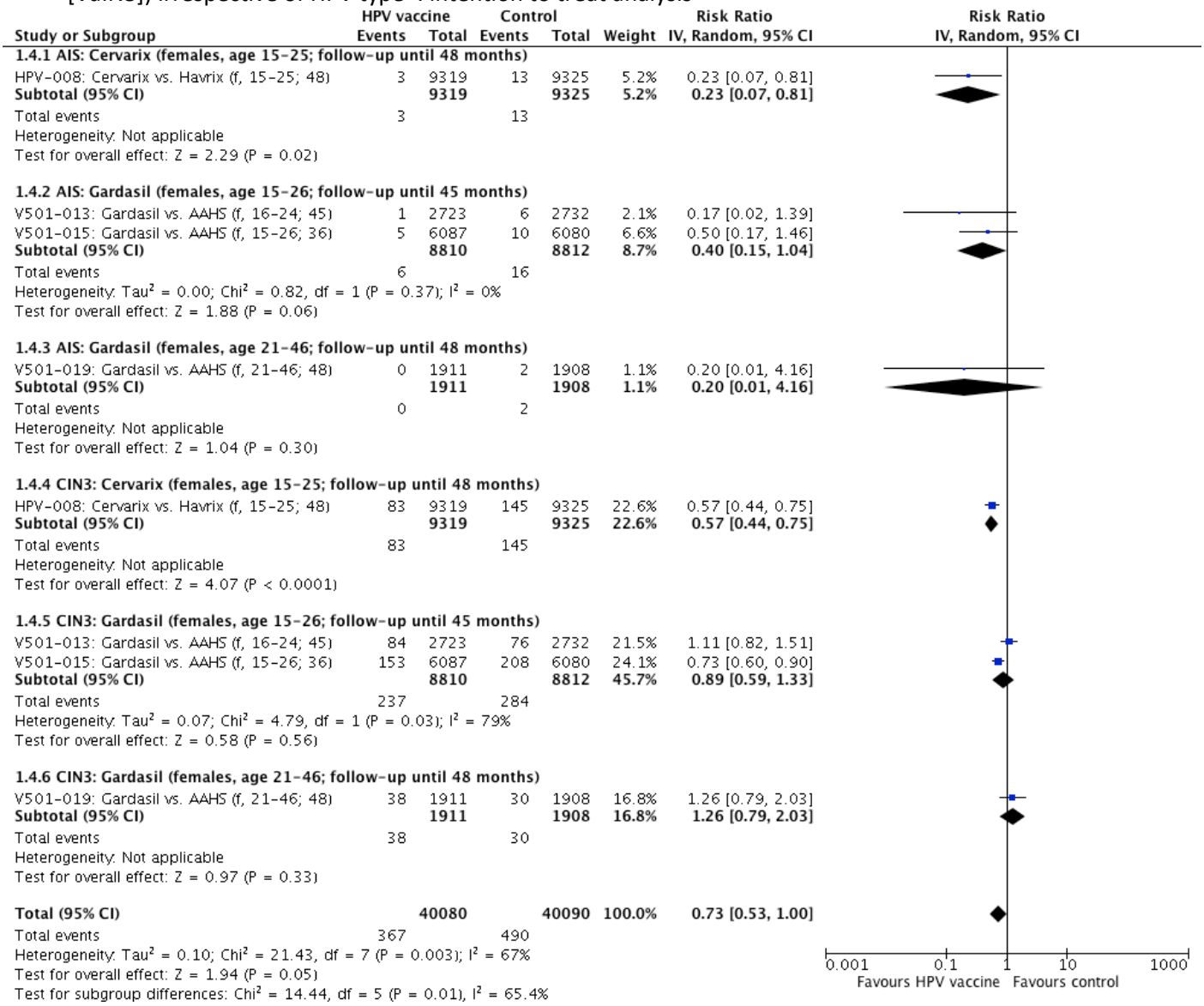
*1.2. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 1.00 [0.10, 9.57]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 3.00 [0.12, 73.48].

1.3. Incidence of HPV-related cancers (anal, cervical, oropharyngeal, penile, vaginal and vulvar) irrespective of HPV type*: intention to treat analysis



*1.3. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 2.24 [0.47, 10.74]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 1.14 [0.19, 6.99]. There were no reported cases of anal or penile cancer.

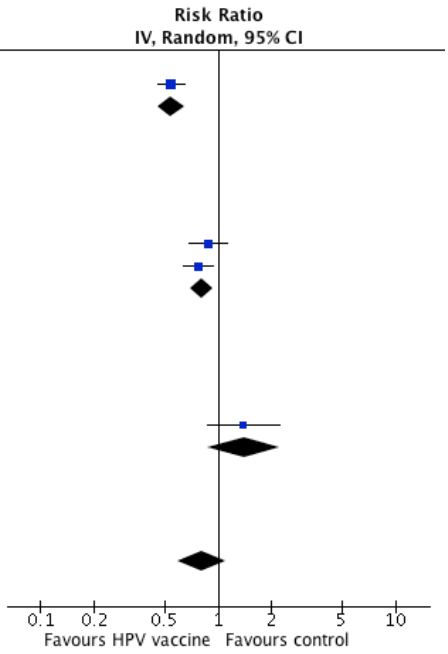
1.4. Incidence of HPV-related carcinoma in situ (anal intraepithelial neoplasia grade 3 [AIN3], cervical adenocarcinoma in situ [AIS], cervical intraepithelial neoplasia grade 3 [CIN3], penile intraepithelial neoplasia grade 3 [PIN3], vaginal intraepithelial neoplasia grade 3 [VIN3] and vulvar intraepithelial neoplasia grade 3 [VaIN3]) irrespective of HPV type*: intention to treat analysis



*1.4. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): **0.45 [0.21, 0.99]**; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 0.87 [0.62, 1.22]. There were no reports of AIN3, PIN3, VIN3 or VaIN3 irrespective of HPV type.

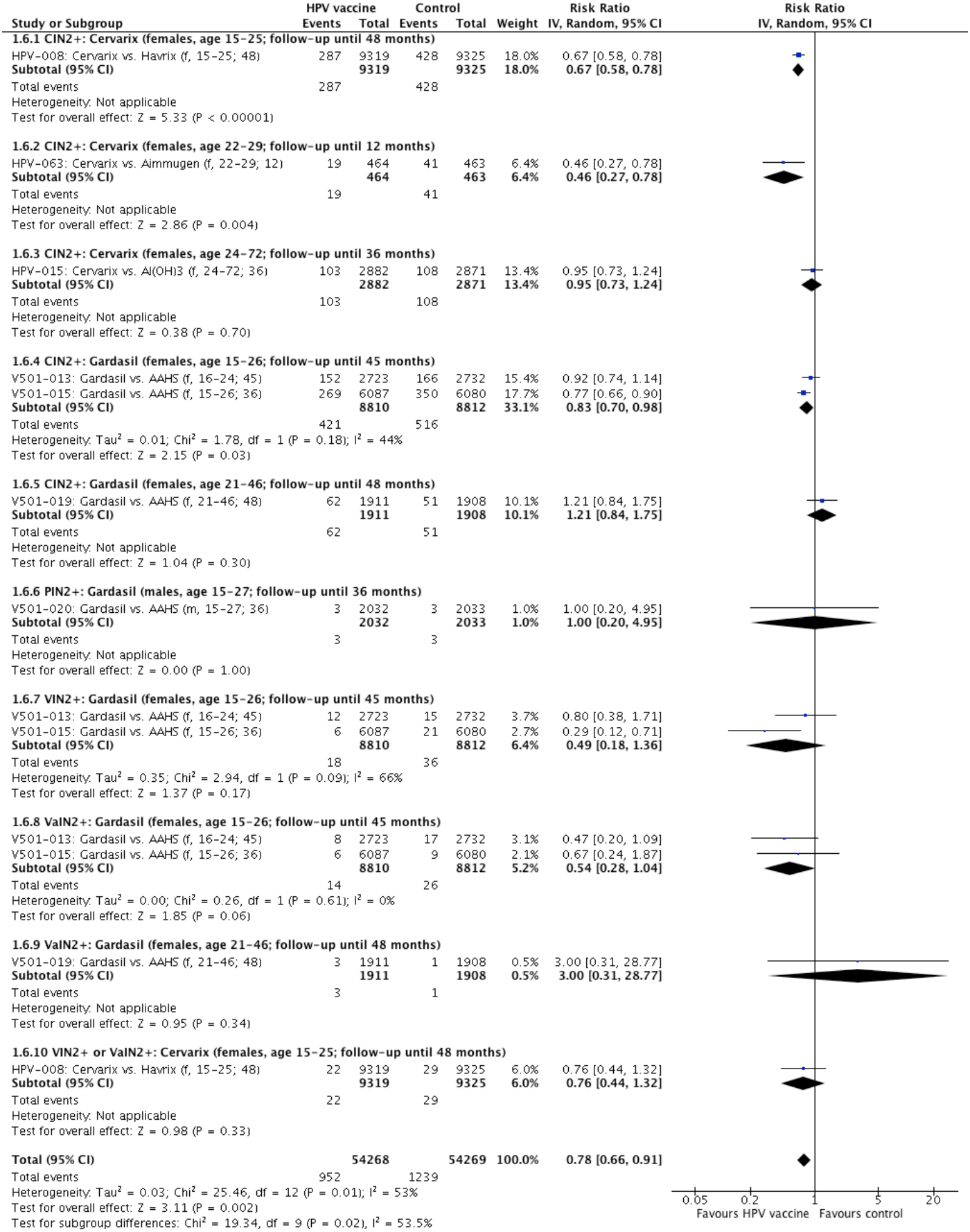
1.5. Incidence of HPV-related moderate intraepithelial neoplasia (anal intraepithelial neoplasia grade 2 [AIN2], cervical intraepithelial neoplasia grade 2 [CIN2], penile intraepithelial neoplasia grade 2 [PIN2], vaginal intraepithelial neoplasia grade 2 [VIN2] and vulvar intraepithelial neoplasia grade 2 [VaIN2]) irrespective of HPV type*: intention to treat analysis

Study or Subgroup	HPV vaccine Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.5.1 CIN2: Cervarix (females, age 15–25; follow-up until 48 months)						
HPV-008: Cervarix vs. Havrix (f, 15–25; 48)	201	9319	370	9325	28.2%	0.54 [0.46, 0.64]
Subtotal (95% CI)		**9319**		**9325**	**28.2%**	**0.54 [0.46, 0.64]**
Total events	201		370			
Heterogeneity: Not applicable						
Test for overall effect: Z = 7.06 (P < 0.00001)						
1.5.2 CIN2: Gardasil (females, age 15–26; follow-up until 45 months)						
V501-013: Gardasil vs. AAHS (f, 16–24; 45)	110	2723	125	2732	25.7%	0.88 [0.69, 1.13]
V501-015: Gardasil vs. AAHS (f, 15–26; 36)	185	6087	238	6080	27.6%	0.78 [0.64, 0.94]
Subtotal (95% CI)		**8810**		**8812**	**53.3%**	**0.81 [0.70, 0.95]**
Total events	295		363			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.64$, df = 1 (P = 0.42); $I^2 = 0\%$						
Test for overall effect: Z = 2.68 (P = 0.007)						
1.5.3 CIN2: Gardasil (females, age 21–46; follow-up until 48 months)						
V501-019: Gardasil vs. AAHS (f, 21–46; 48)	42	1911	30	1908	18.5%	1.40 [0.88, 2.22]
Subtotal (95% CI)		**1911**		**1908**	**18.5%**	**1.40 [0.88, 2.22]**
Total events	42		30			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.41 (P = 0.16)						
Total (95% CI)		**20040**		**20045**	**100.0%**	**0.81 [0.59, 1.11]**
Total events	538		763			
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 21.50$, df = 3 (P < 0.0001); $I^2 = 86\%$						
Test for overall effect: Z = 1.31 (P = 0.19)						
Test for subgroup differences: $Chi^2 = 20.86$, df = 2 (P < 0.0001), $I^2 = 90.4\%$						



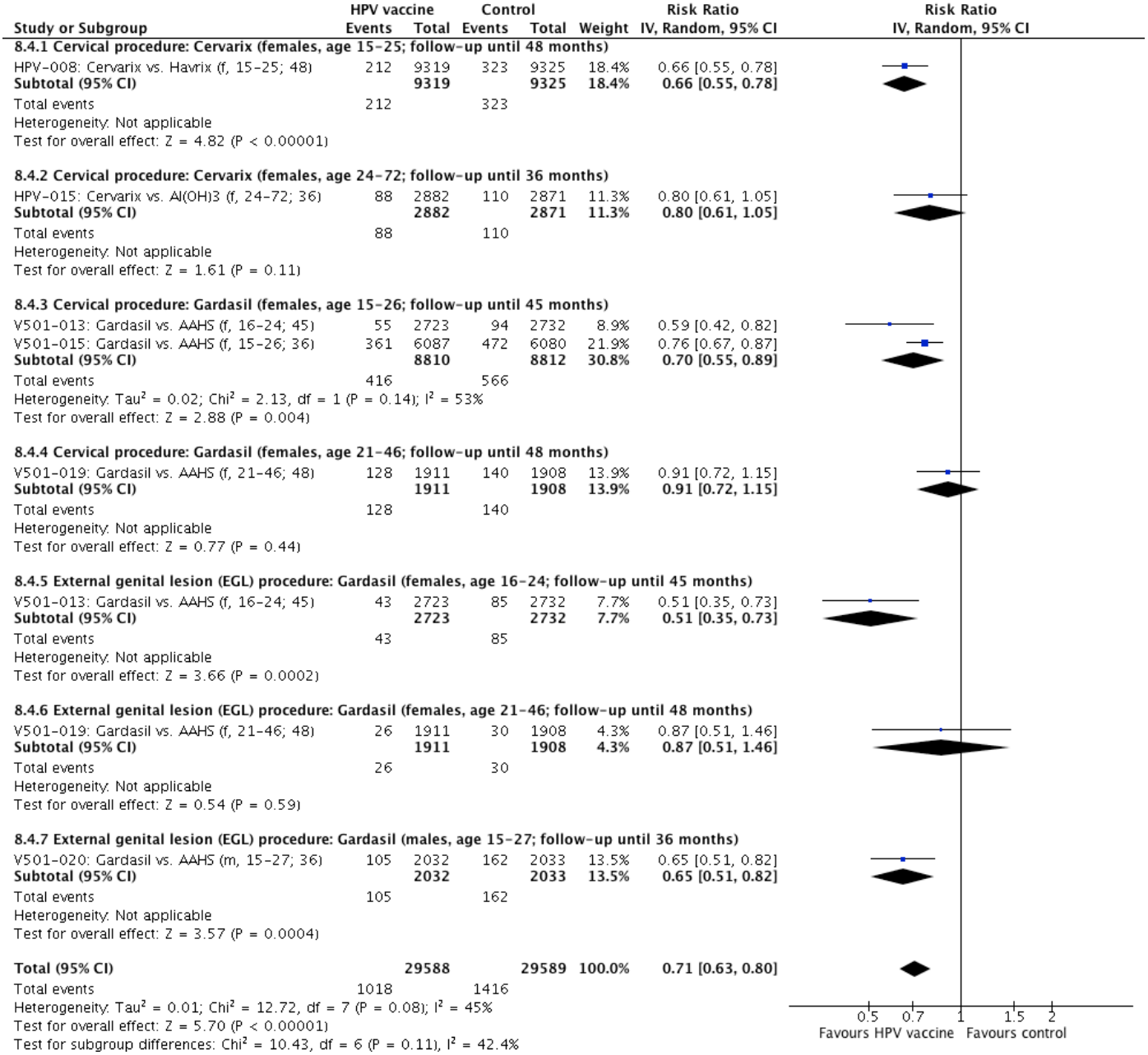
*1.5. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): **0.54 [0.46, 0.64]**; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 0.92 [0.70, 1.19]. There were no reports of AIN2, PIN2, VIN2 or VaIN2 irrespective of HPV type.

1.6. Incidence of HPV-related moderate intraepithelial neoplasia or worse (AIN2$^+$, CIN2$^+$, PIN2$^+$, VIN2$^+$, VaIN2$^+$) irrespective of HPV type*: intention to treat analysis



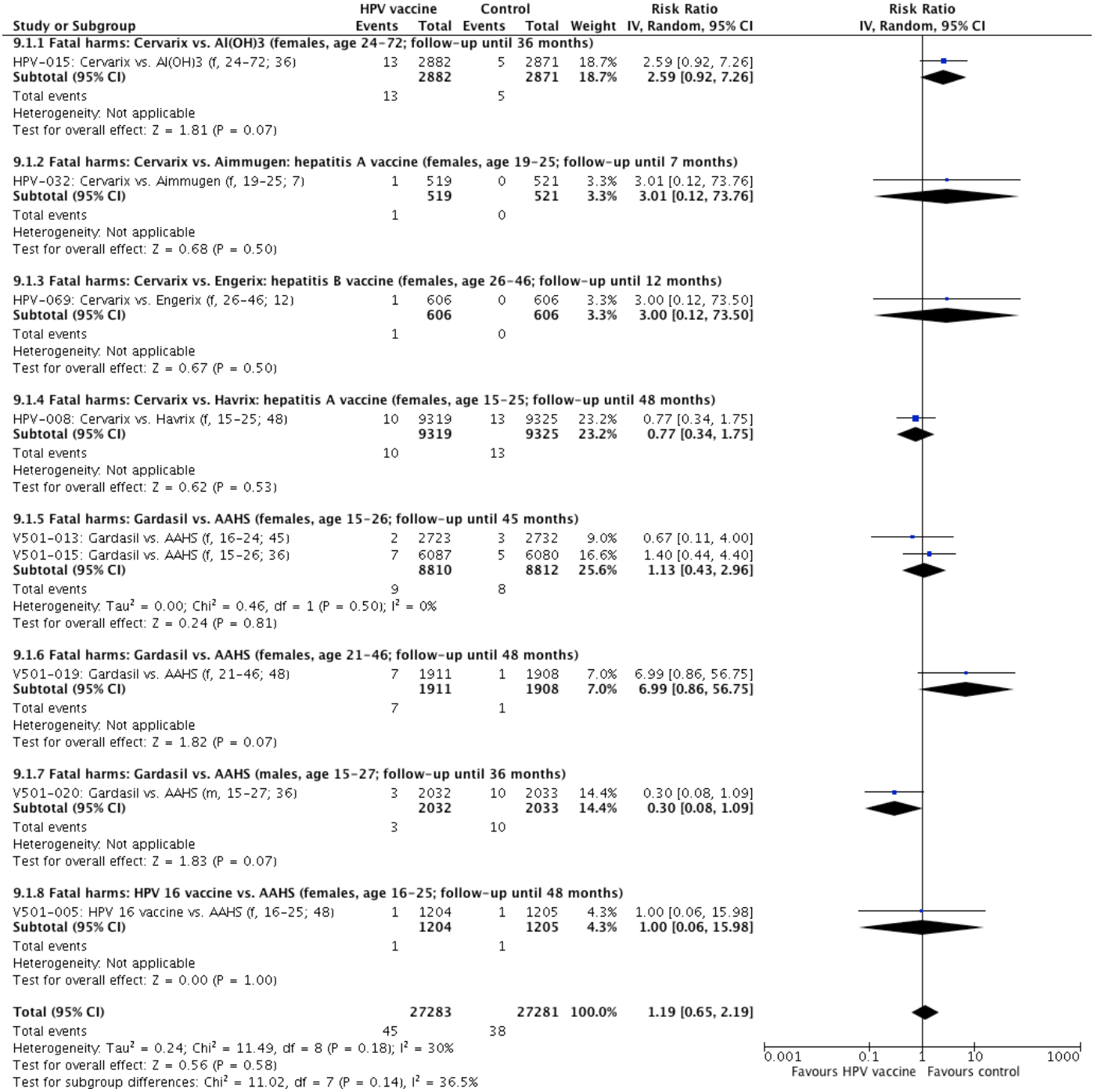
*1.6. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): **0.72 [0.55, 0.93]**; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 0.82 [0.66, 1.02]. There were no reports of AIN2$^+$ irrespective of HPV type.

1.7. Number of treatment procedures (both surgical and non-surgical treatment) due to HPV-related diseases irrespective of HPV type*: intention to treat analysis



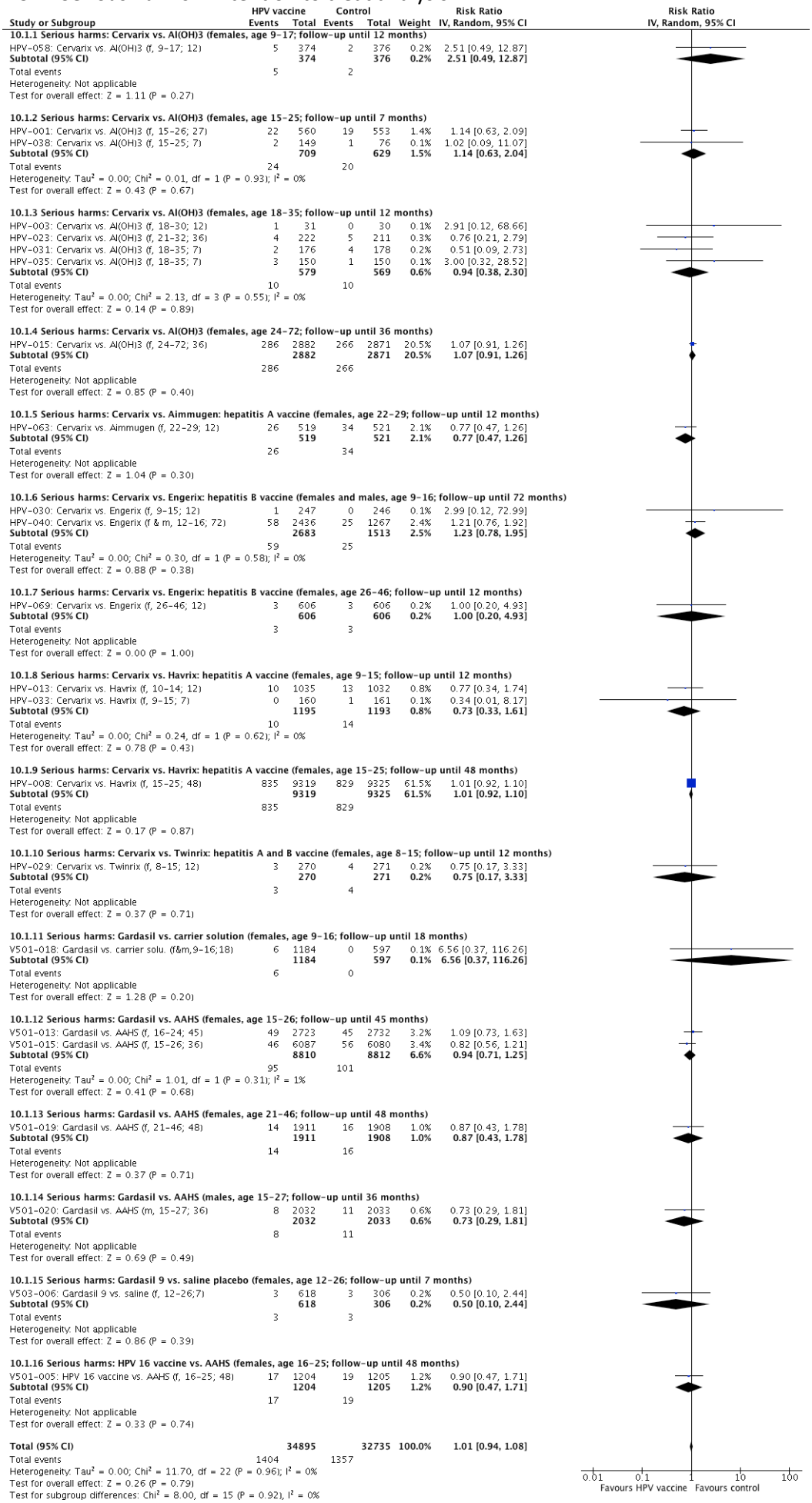
*1.7. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): **0.70 [0.59, 0.84]**; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): **0.71 [0.60, 0.83]**. Only cervical procedure: 844 in the HPV vaccine group vs. 1,139 in the control group, risk ratio **0.74 [0.65, 0.84]**; only EGL procedure: 174 vs. 277, risk ratio **0.63 [0.50, 0.80]**.

1.8. Fatal harms*: intention to treat analysis



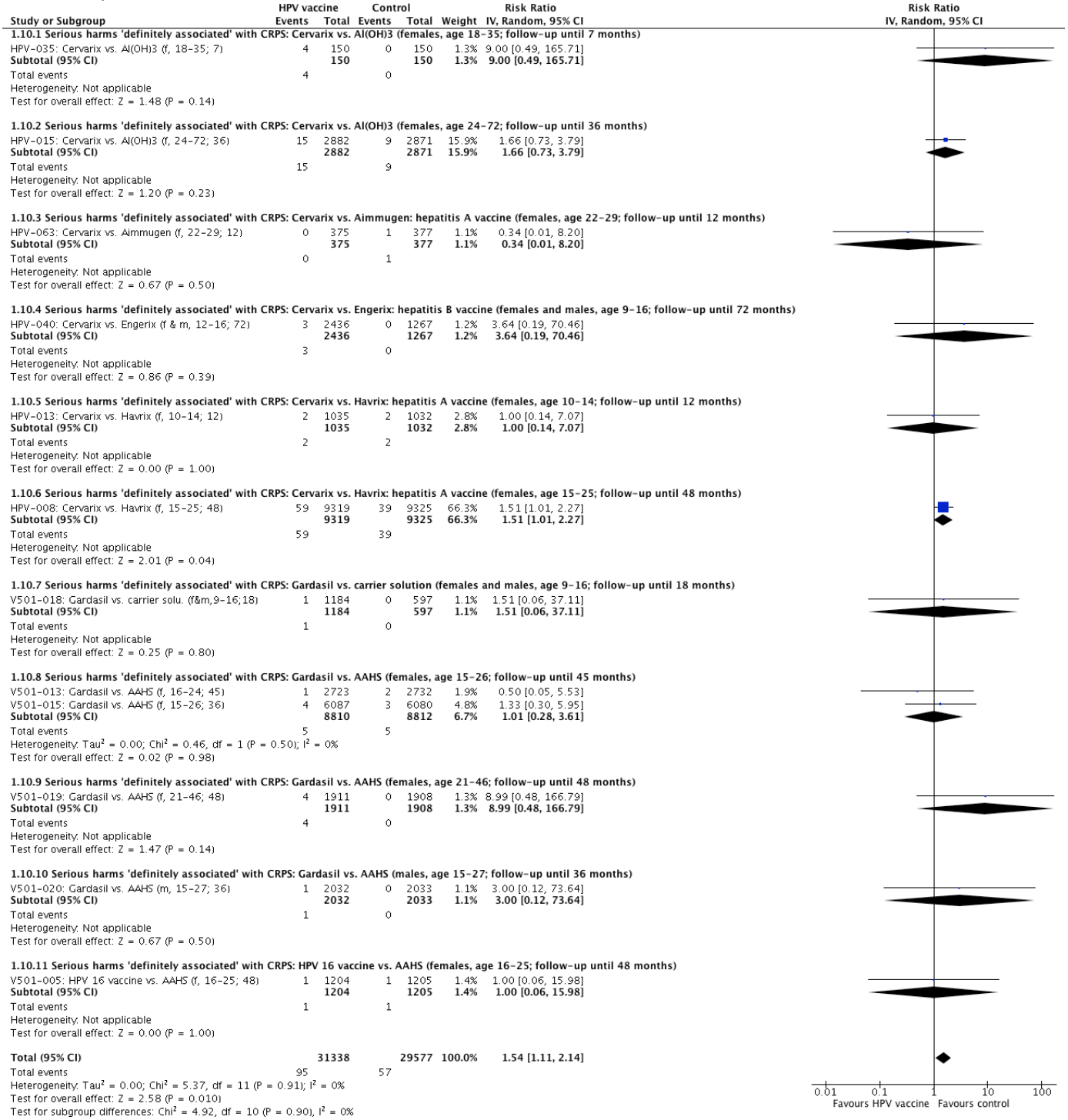
*1.8. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 1.43 [0.65, 3.15]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 1.08 [0.40, 2.96]. The most common fatal serious harms were: 'road traffic accident' (five in the HPV vaccine group and seven in the control group, risk ratio 0.77 [0.24, 2.46]); 'completed suicide' (four and eight, risk ratio 0.58 [0.15, 2.19]); 'cardiorespiratory arrest' (three and two, risk ratio 0.99 [0.13, 7.65]); 'gunshot wound' (two and three, risk ratio 0.74 [0.09, 5.85]); and 'homicide' (two and two, risk ratio 0.95 [0.14, 6.50]). The fatal serious harms most increased by the HPV vaccines were: 'cardiac arrest' (two in the HPV vaccine group and none in the control group, risk ratio 3.00 [0.31, 28.82]); 'traumatic intracranial haemorrhage' (two and none, risk ratio 3.00 [0.31, 28.82]); 'systemic lupus erythematosus' (two and none, risk ratio 3.00 [0.31, 28.82]); 'metastases to lung' (two and none, risk ratio 3.00 [0.31, 28.82]); and 'renal failure acute' (two and none, risk ratio 3.00 [0.31, 28.82]). The fatal serious harms most decreased by the HPV vaccines were: 'completed suicide' (four in the HPV vaccine group and eight in the control group, risk ratio 0.58 [0.15, 2.19]); and 'road traffic accident' (five and seven, risk ratio 0.77 [0.24, 2.46]).

1.9. Serious harms*: intention to treat analysis



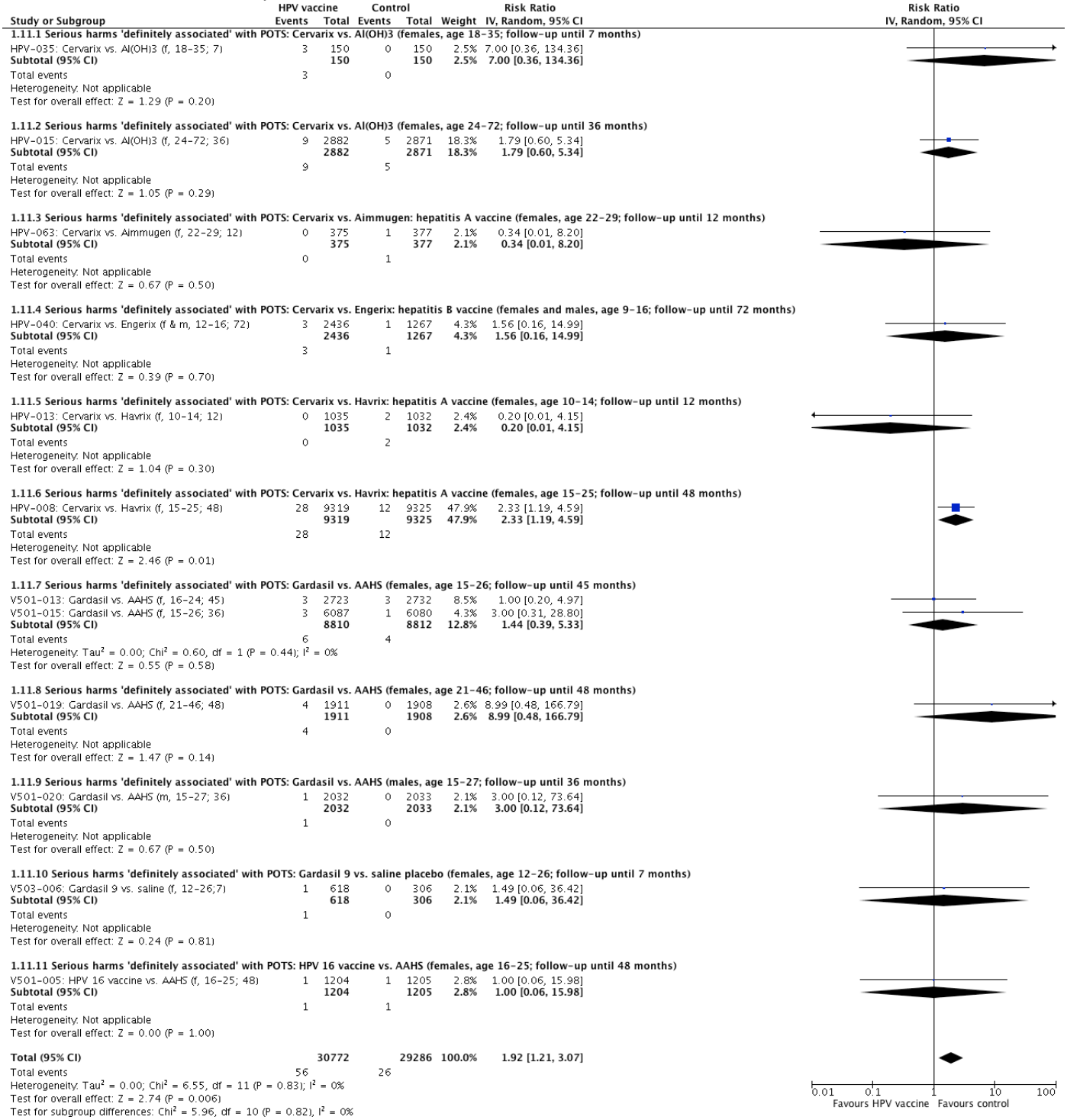
*1.9. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 1.02 [0.95, 1.10]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 0.91 [0.73, 1.15].

1.10. Serious harms judged as 'definitely associated'* with chronic regional pain syndrome (CRPS): intention to treat analysis



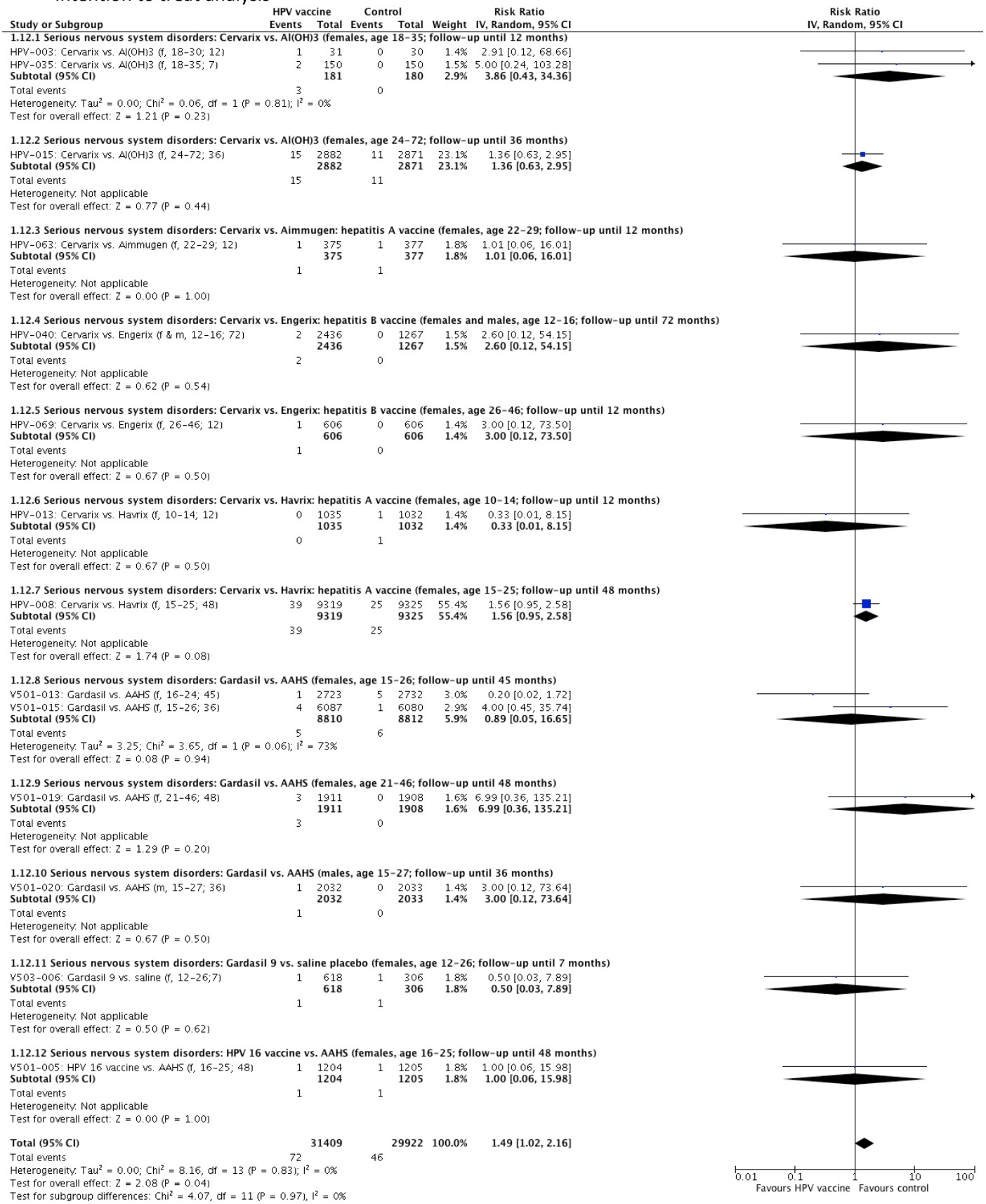
*1.10. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): **1.55 [1.09, 2.20]**; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 1.47 [0.56, 3.89]. We asked a physician with clinical expertise in CRPS to assess the reported MedDRA preferred terms as 'definitely,' 'probably,' 'probably not' or 'definitely not' associated with CRPS. We sent an Excel sheet to the physician with all the reported MedDRA terms. The physician was blinded, as the Excel sheet contained no outcome data. When the physician had assessed all the MedDRA terms, we synthesized the data for those MedDRA terms that the physician judged 'definitely' associated with CRPS and compared it to the reported serious harms.

1.11. Serious harms judged as ‘definitely associated’* with postural orthostatic tachycardia syndrome (POTS): intention to treat analysis



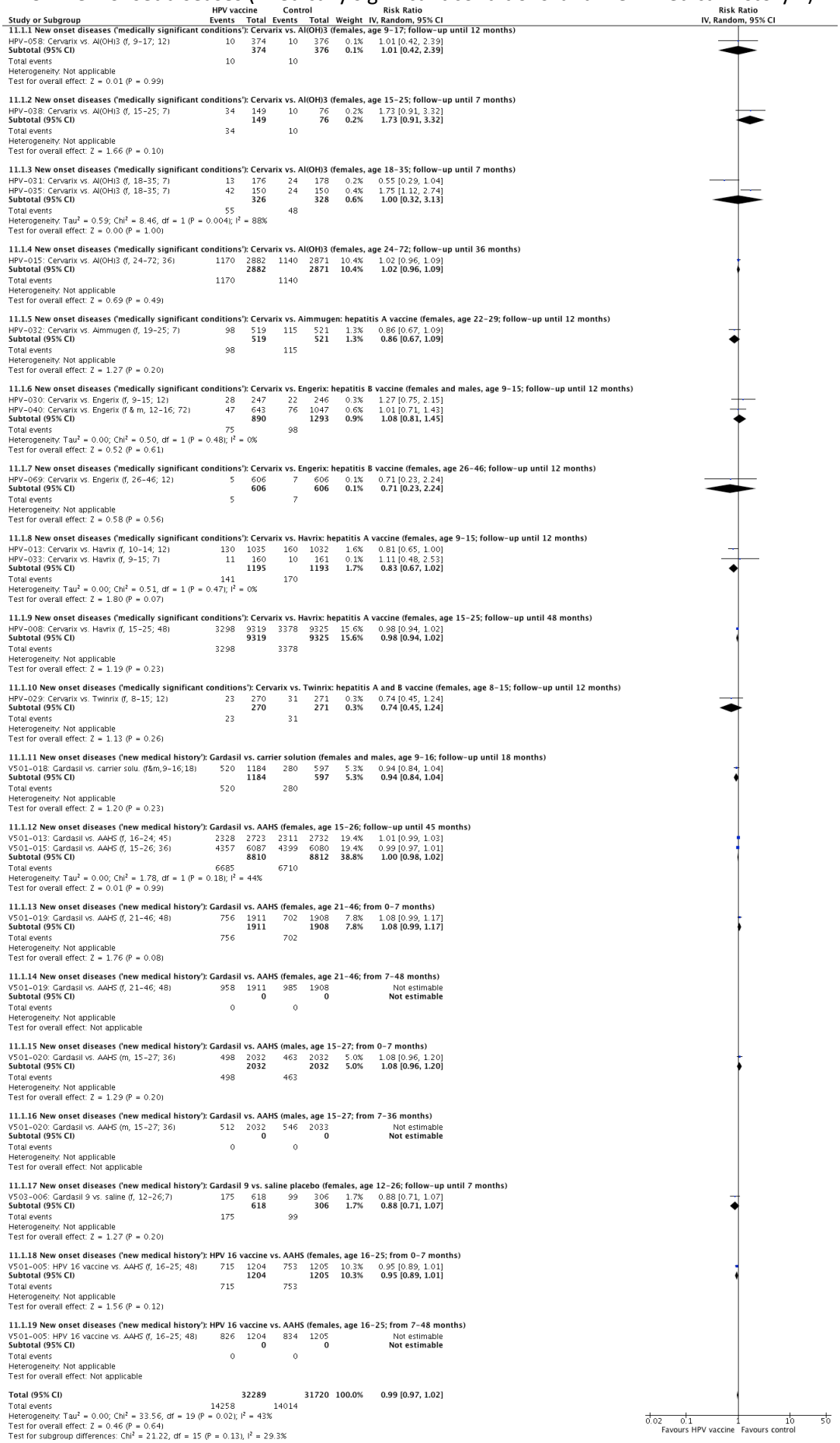
*1.11. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): **1.95 [1.15, 3.32]**; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 1.82 [0.68, 4.89]. We asked a physician with clinical expertise in POTS to assess the reported MedDRA preferred terms as 'definitely,' 'probably,' 'probably not' or 'definitely not' associated with POTS. We sent an Excel sheet to the physician with all the reported MedDRA terms. The physician was blinded, as the Excel sheet contained no outcome data. When the physician had assessed all the MedDRA terms, we synthesized the data for those MedDRA terms that the physician judged 'definitely' associated with POTS and compared it to the reported serious harms.

1.12. Serious harms reported within the MedDRA system organ class 'nervous system disorders (10029205)'*: intention to treat analysis



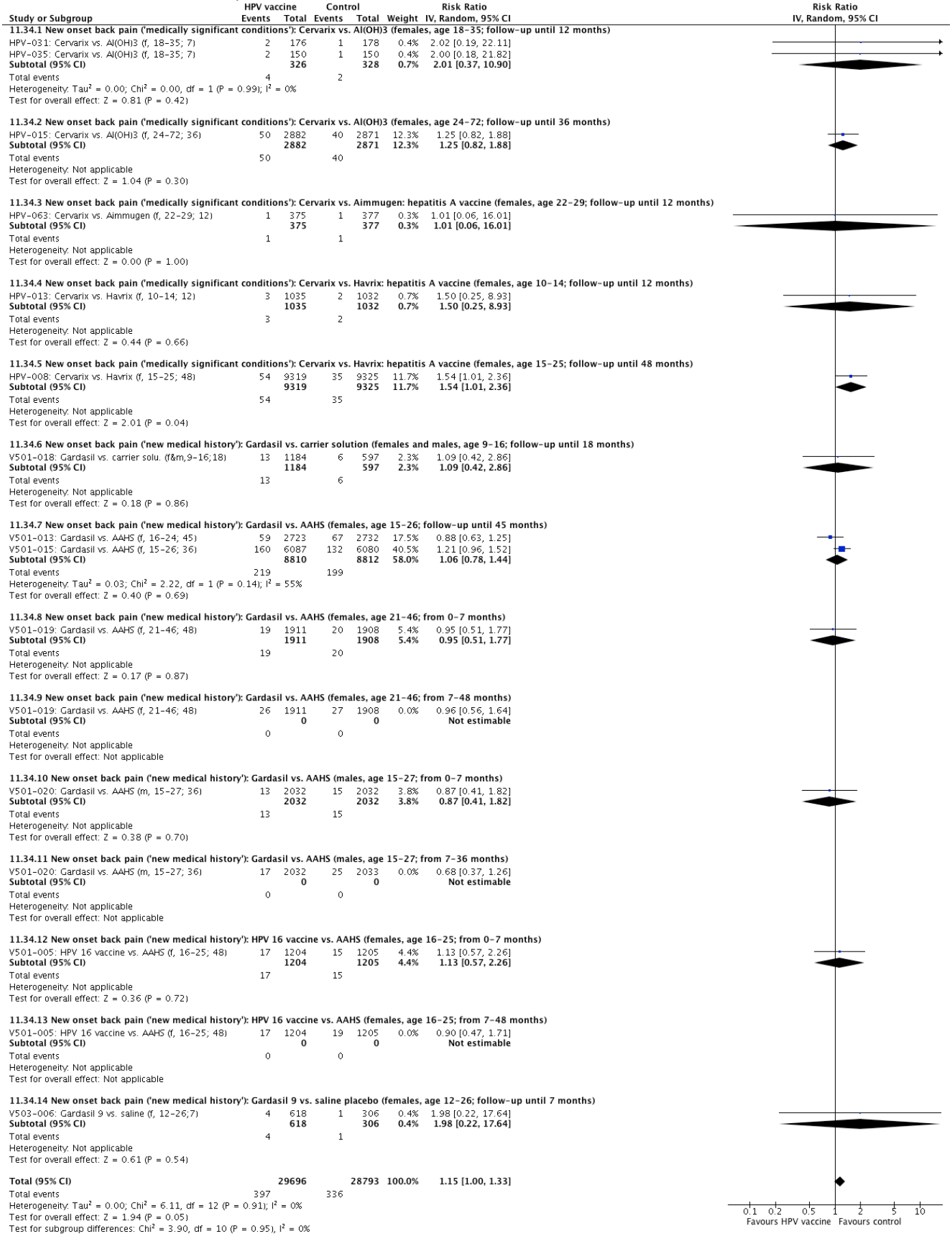
*1.12. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): **1.53 [1.03, 2.28]**; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 1.25 [0.39, 3.97].

1.13. New onset diseases ('medically significant conditions' and 'new medical history'*): intention to treat analysis



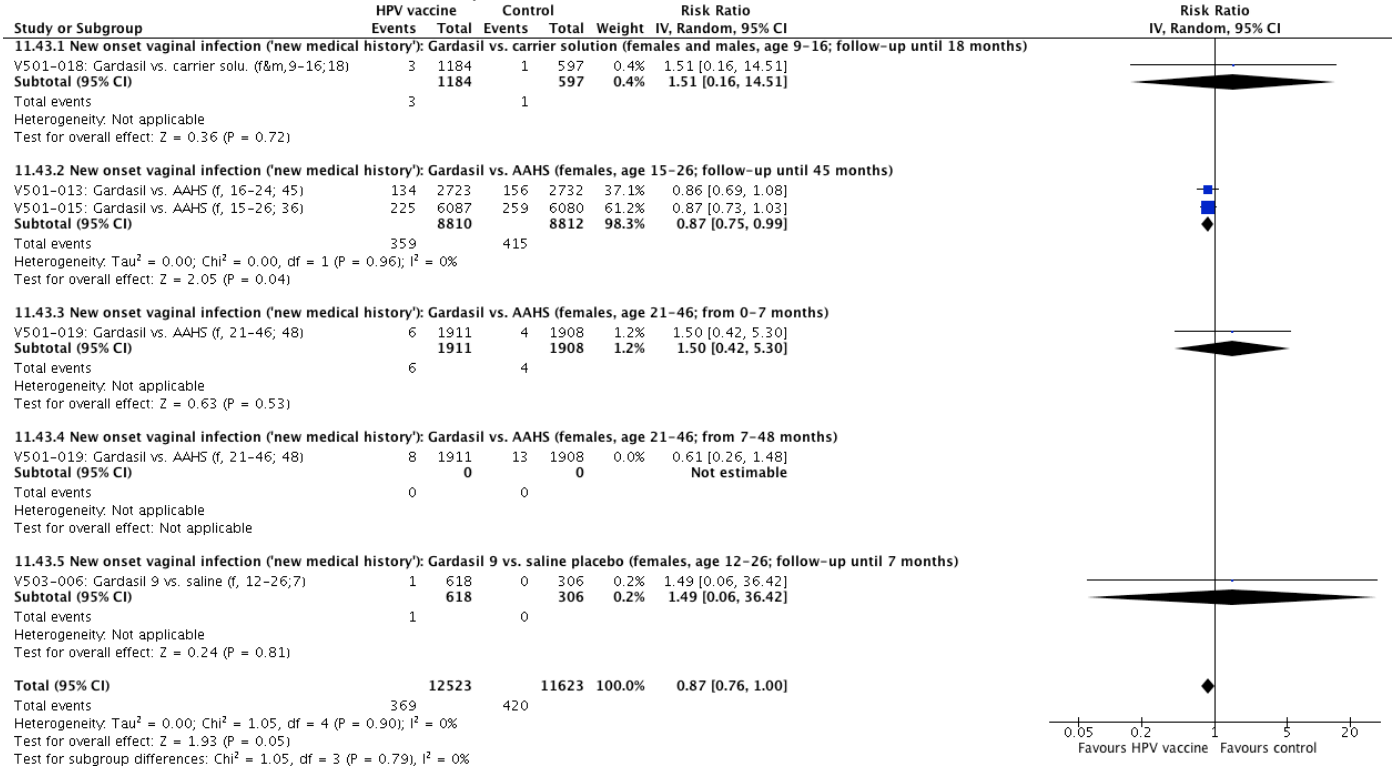
*1.13. Risk ratio for 'medically significant conditions' (GlaxoSmithKline): 0.98 [0.90, 1.06]; risk ratio for 'new medical history' (Merck Sharp & Dohme): 1.00 [0.97, 1.03]; risk ratio for the follow-up periods for the trials V501-005, V501-019 and V501-020 (Merck Sharp & Dohme): 0.98 [0.94, 1.01] (2,296 participants with new medical history in the HPV vaccine group vs. 2,365 participants with new medical history in the control group. The trials V501-005, V501-019 and V501-020 split the reporting of new onset diseases into the vaccination period and the follow-up period. To avoid double counting of participants in the total risk ratio estimate, we only included the new onset diseases reported in the vaccination period for the trials V501-005, V501-019 and V501-020).

1.14. New onset diseases most associated with the HPV vaccines ('medically significant conditions'*) - 'back pain': intention to treat analysis



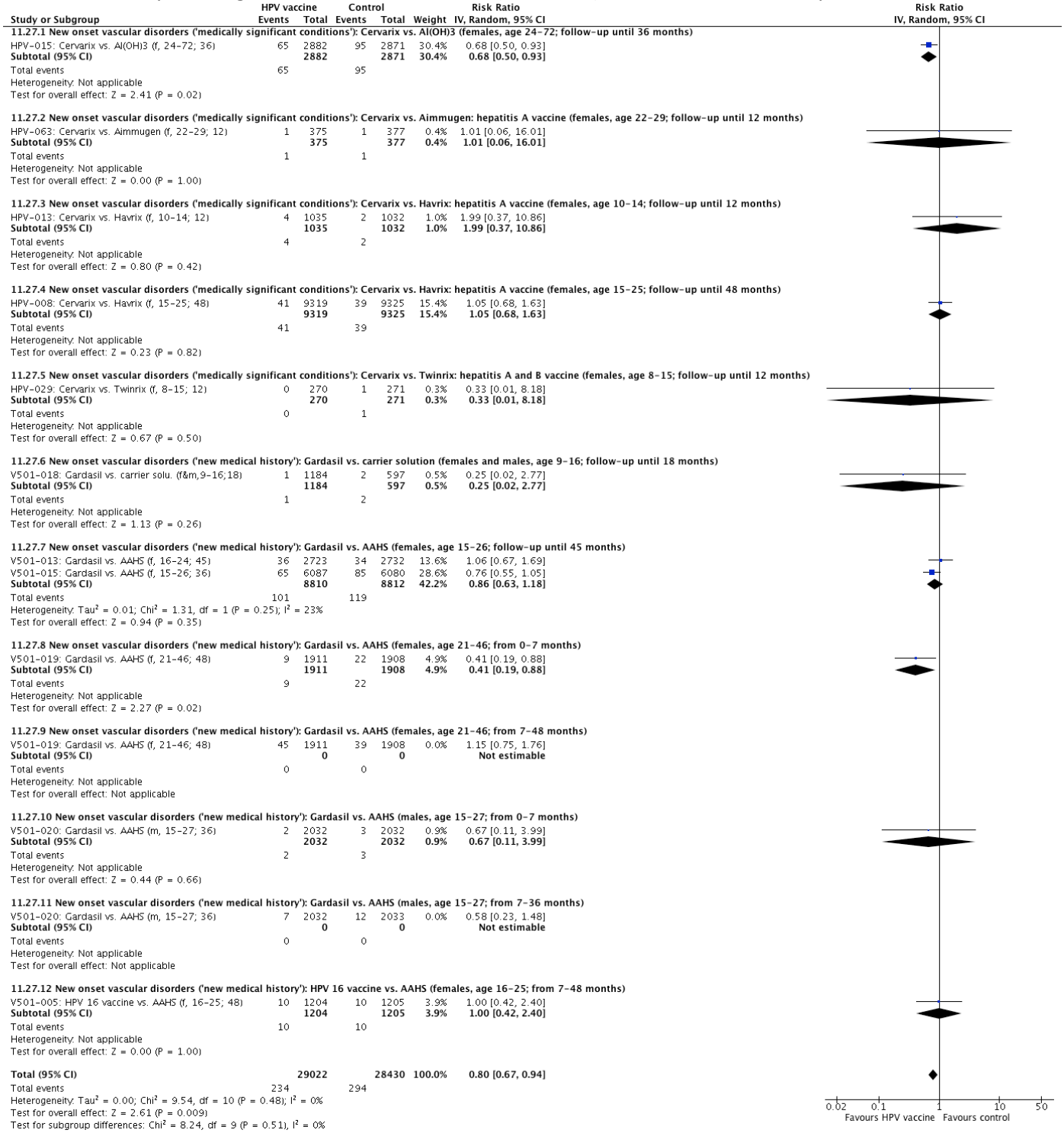
*1.14. Risk ratio for 'medically significant conditions' (GlaxoSmithKline): **1.40 [1.05, 1.86]**; risk ratio for 'new medical history' (Merck Sharp & Dohme): 1.08 [0.91, 1.28]; risk ratio for the follow-up periods for the trials V501-005, V501-019 and V501-020: 0.85 [0.60, 1.19]. The trials V501-005, V501-019 and V501-020 split the reporting of new onset diseases into the vaccination period and the follow-up period. To avoid double counting of participants in the total risk ratio estimate, we only included the new onset diseases reported in the vaccination period for the trials V501-005, V501-019 and V501-020.

1.15. New onset diseases most inversely associated with the HPV vaccines (‘new medical history’*) - ‘vaginal infection’: intention to treat analysis



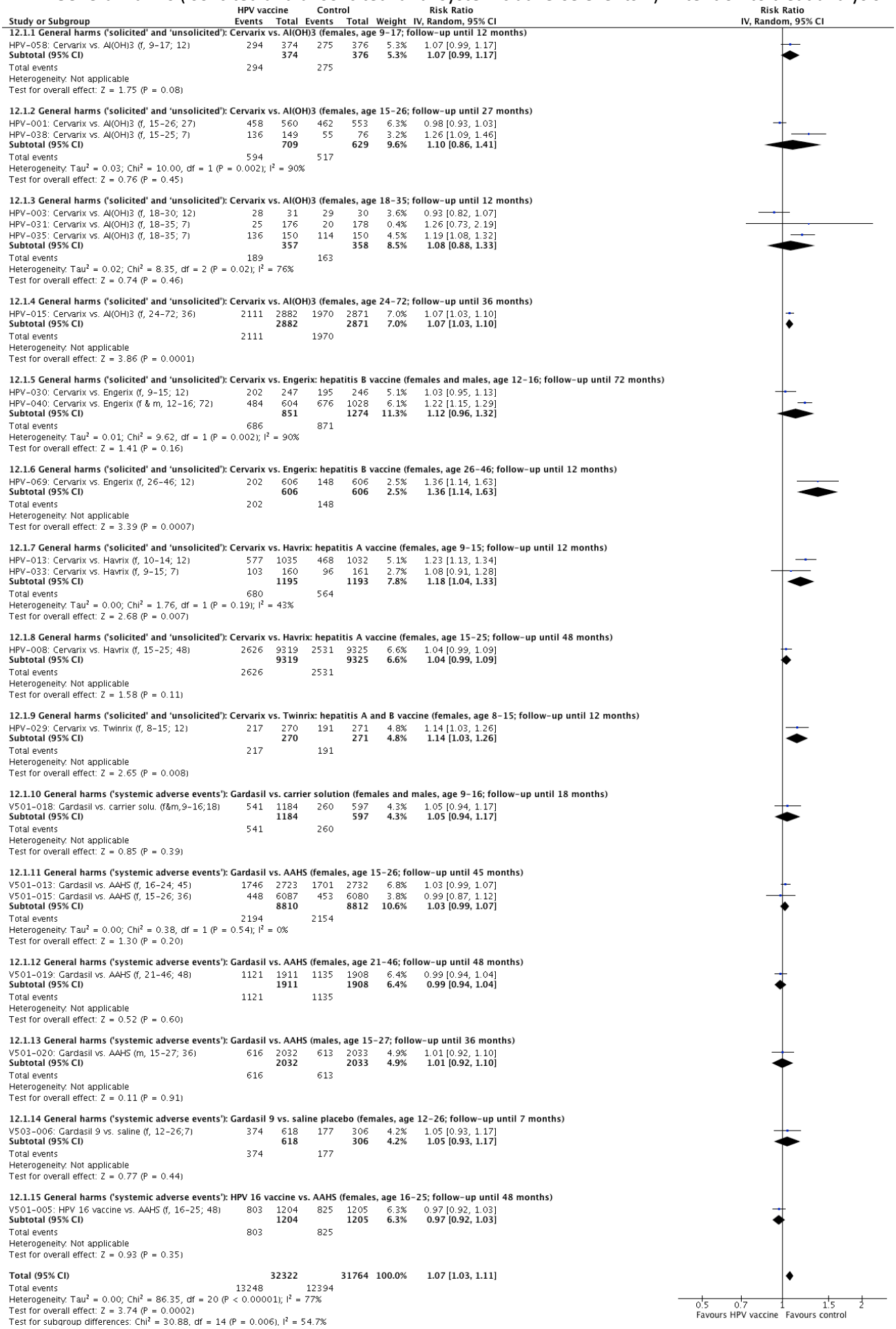
*1.15. Risk ratio for 'medically significant conditions’ (GlaxoSmithKline): not applicable; risk ratio for ‘new medical history’ (Merck Sharp & Dohme): **0.87 [0.76, 1.00]**; risk ratio for the follow-up period for the trial V501-019: 0.61 [0.26, 1.48]. The trial V501-019 split the reporting of new onset diseases into the vaccination period and the follow-up period. To avoid double counting of participants in the total risk ratio estimate, we only included the new onset diseases reported in the vaccination period for the trial V501-019.

1.16. New onset diseases ('medically significant conditions' and 'new medical history'*) reported within the MedDRA system organ class 'vascular disorders (10047065)': intention to treat analysis



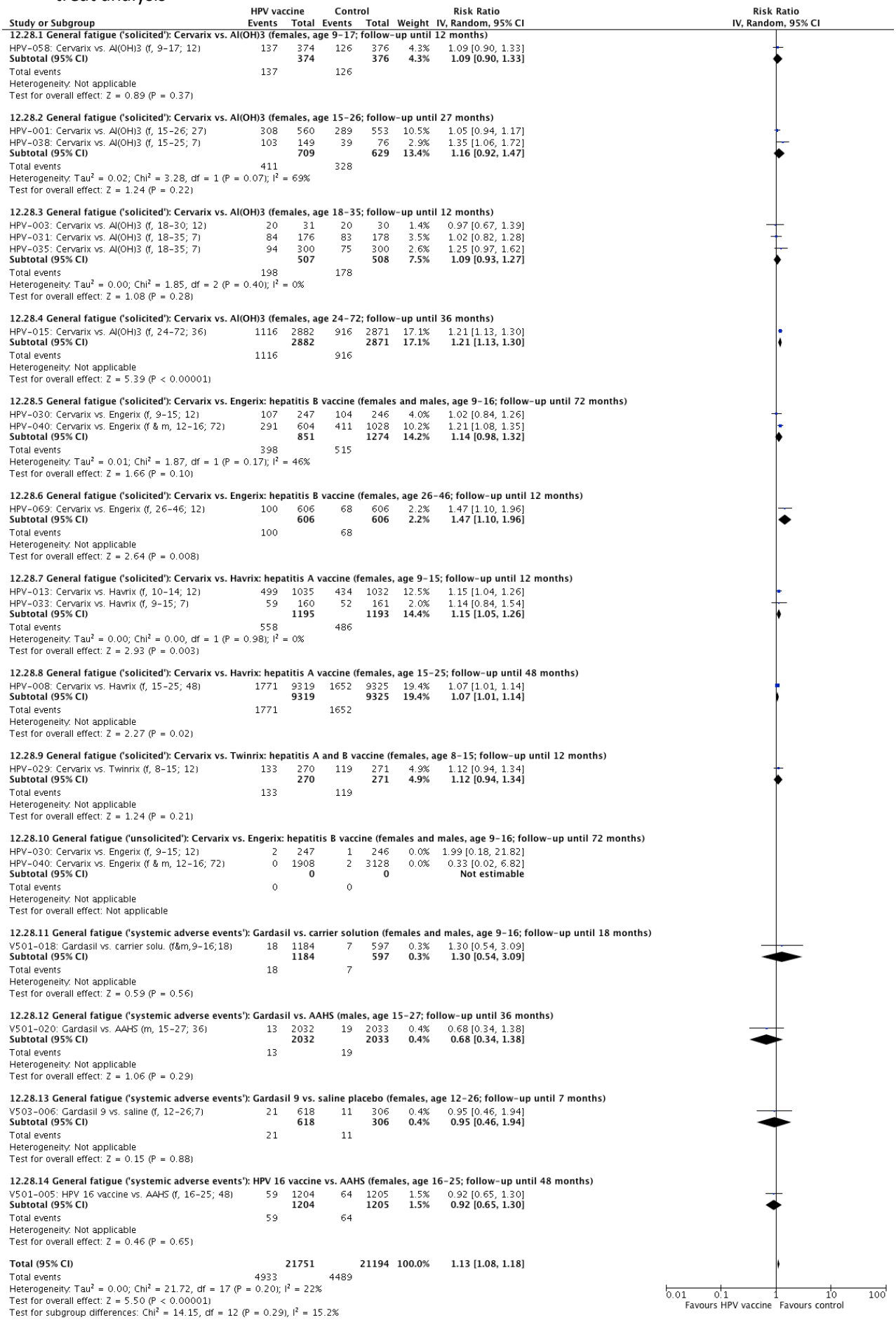
*1.16. Risk ratio for 'medically significant conditions' (GlaxoSmithKline): 0.80 [0.63, 1.03]; risk ratio for 'new medical history' (Merck Sharp & Dohme): 0.78 [0.60, 1.03]; risk ratio for the follow-up periods for the trials V501-019 and V501-020: 0.93 [0.51, 1.73]. The trials V501-019 and V501-020 split the reporting of new onset diseases into the vaccination period and the follow-up period. To avoid double counting of participants in the total risk ratio estimate, we only included the new onset diseases reported in the vaccination period for the trials V501-019 and V501-020.

1.17. General harms ('solicited and unsolicited' and 'systemic adverse events'*): intention to treat analysis



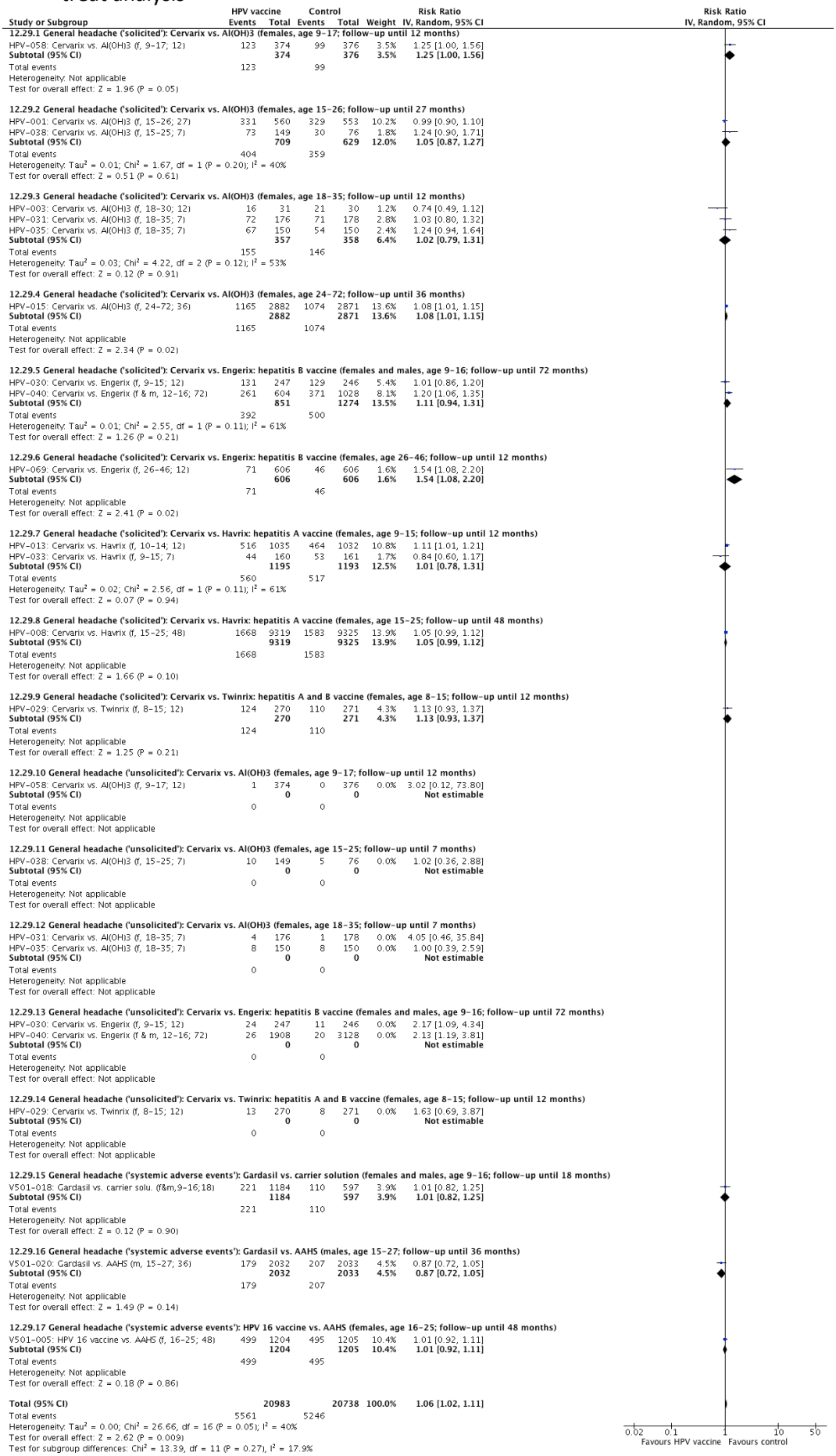
*1.17. Risk ratio for 'solicited and solicited' (GlaxoSmithKline): **1.11 [1.06, 1.16]**; risk ratio for 'systemic adverse events' (Merck Sharp & Dohme): 1.01 [0.98, 1.03]. The total numbers of participants with general harms in GlaxoSmithKline studies were reported as 'solicited [SGAE] and unsolicited [UGAE]' combined.

1.18. General harms most associated with the HPV vaccines ('solicited' and 'unsolicited') - 'fatigue': intention to treat analysis



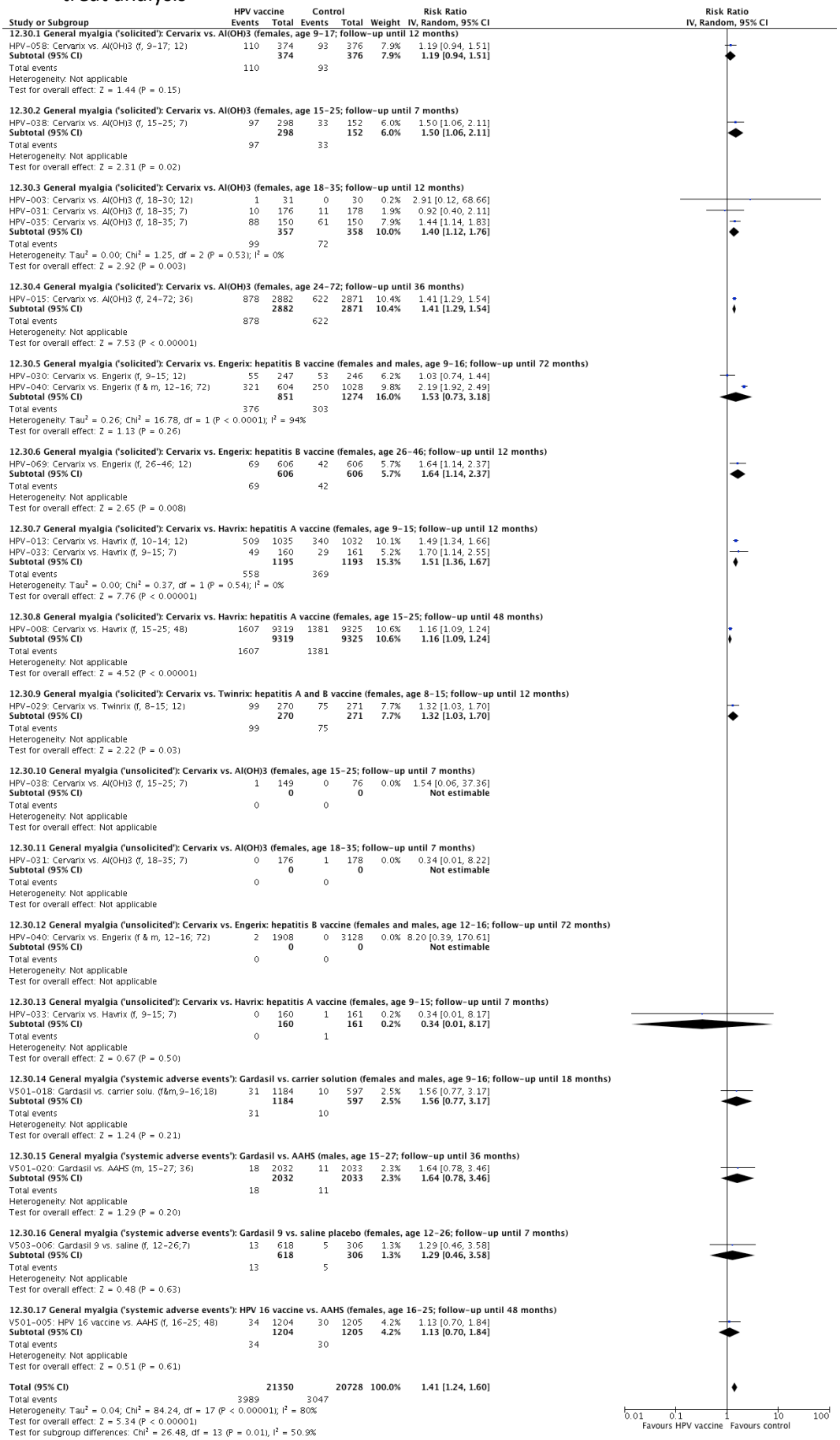
*1.18. Risk ratio for 'solicited' (GlaxoSmithKline): **1.14 [1.09, 1.19]**; risk ratio for 'unsolicited' (GlaxoSmithKline): 1.00 [0.15, 6.53]; risk ratio for 'systemic adverse events' (Merck Sharp & Dohme): 0.92 [0.70, 1.20]. To avoid double counting of participants in the total risk ratio estimate, we excluded the 'unsolicited' adverse events from total risk ratio estimate for studies that reported 'solicited' adverse events.

1.19. General harms most associated with the HPV vaccines ('solicited' and 'unsolicited') - 'headache': intention to treat analysis



*1.19. Risk ratio for 'solicited' (GlaxoSmithKline): **1.08 [1.03, 1.14]**; risk ratio for 'unsolicited' (GlaxoSmithKline): **1.76 [1.26, 2.47]**; risk ratio for 'systemic adverse events' (Merck Sharp & Dohme): 0.98 [0.90, 1.07]. To avoid double counting of participants in the total risk ratio estimate, we excluded the 'unsolicited' adverse events from total risk ratio estimate for studies that reported 'solicited' adverse events.

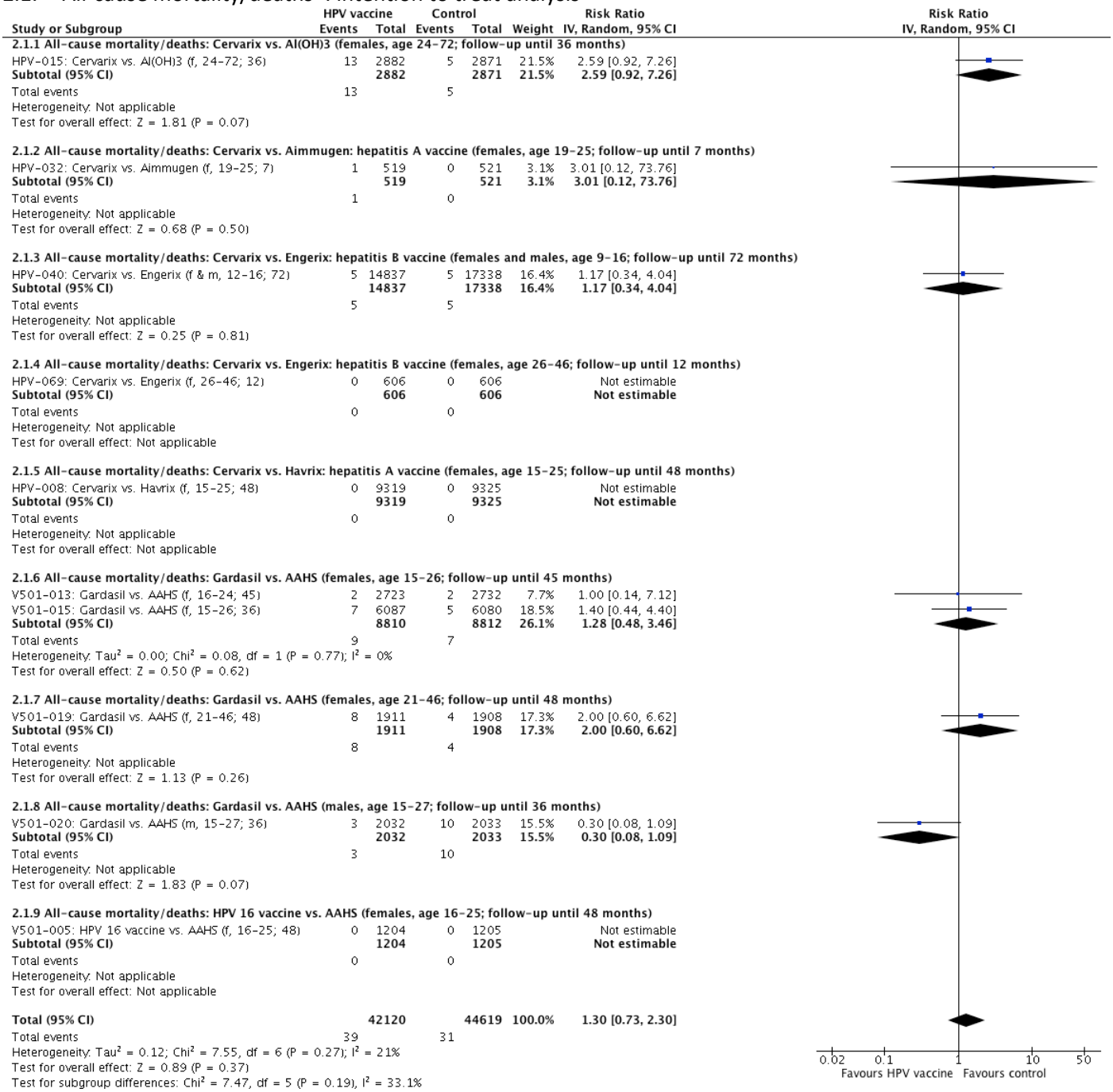
1.20. General harms most associated with the HPV vaccines ('solicited' and 'unsolicited') - 'myalgia': intention to treat analysis



*1.20. Risk ratio for 'solicited' (GlaxoSmithKline): **1.42 [1.24, 1.63]**; risk ratio for 'unsolicited' (GlaxoSmithKline): 1.15 [0.24, 5.57]; risk ratio for 'systemic adverse events' (Merck Sharp & Dohme): 1.33 [0.95, 1.85]. To avoid double counting of participants in the total risk ratio estimate, we excluded the 'unsolicited' adverse events from total risk ratio estimate for studies that reported 'solicited' adverse events.

2. Trial register entries

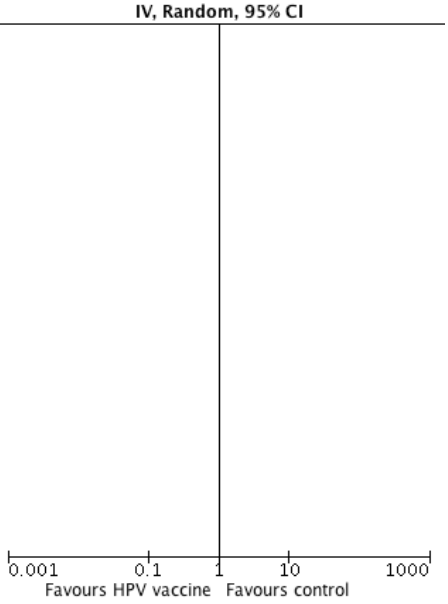
2.1. All-cause mortality/deaths*: intention to treat analysis



*2.1. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 1.92 [0.89, 4.15]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 0.98 [0.41, 2.33].

2.2. Mortality/deaths from HPV-related cancers (anal, cervical, oropharyngeal, penile, vaginal and vulvar) irrespective of HPV type: intention to treat analysis

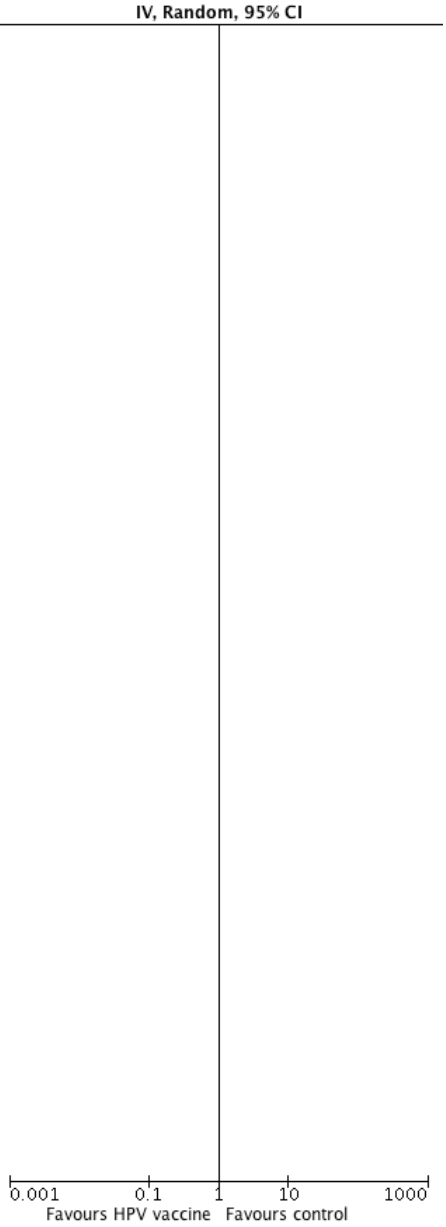
Study or Subgroup	HPV vaccine Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
2.2.1 Cervical cancer: Cervarix (females, age 24-72; follow-up until 36 months)						
HPV-015: Cervarix vs. Al(OH)3 (f, 24-72; 36)	0	2882	0	2871		Not estimable
Subtotal (95% CI)		**2882**		**2871**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.2.2 Oropharyngeal cancer: Cervarix (females, age 24-72; follow-up until 36 months)						
HPV-015: Cervarix vs. Al(OH)3 (f, 24-72; 36)	0	2882	0	2871		Not estimable
Subtotal (95% CI)		**2882**		**2871**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.2.3 Oropharyngeal cancer: Gardasil (females, age 21-46; follow-up until 48 months)						
V501-019: Gardasil vs. AAHS (f, 21-46; 48)	0	1911	0	1908		Not estimable
Subtotal (95% CI)		**1911**		**1908**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**7675**		**7650**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



*2.2. Risk ratio for 'medically significant conditions' (GlaxoSmithKline): not applicable; risk ratio for 'new medical history' (Merck Sharp & Dohme): not applicable.

2.3. Incidence of HPV-related cancers (anal, cervical, oropharyngeal, penile, vaginal and vulvar) irrespective of HPV type: intention to treat analysis

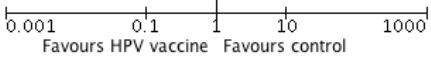
Study or Subgroup	HPV vaccine Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
2.3.1 Cervical cancer: Cervarix (females, age 24-72; follow-up until 36 months)						
HPV-015: Cervarix vs. Al(OH)3 (f, 24-72; 36)	0	2882	0	2871		Not estimable
Subtotal (95% CI)		**2882**		**2871**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.3.2 Cervical cancer: Gardasil (females, age 21-46; follow-up until 48 months)						
V501-019: Gardasil vs. AAHS (f, 21-46; 48)	0	1911	0	1908		Not estimable
Subtotal (95% CI)		**1911**		**1908**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.3.3 Oropharyngeal cancer: Cervarix (females, age 24-72; follow-up until 36 months)						
HPV-015: Cervarix vs. Al(OH)3 (f, 24-72; 36)	0	2882	0	2871		Not estimable
Subtotal (95% CI)		**2882**		**2871**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.3.4 Oropharyngeal cancer: Gardasil (females, age 21-46; follow-up until 48 months)						
V501-019: Gardasil vs. AAHS (f, 21-46; 48)	0	1911	0	1908		Not estimable
Subtotal (95% CI)		**1911**		**1908**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.3.5 Vaginal cancer: Cervarix (females, age 24-72; follow-up until 36 months)						
HPV-015: Cervarix vs. Al(OH)3 (f, 24-72; 36)	0	2882	0	2871		Not estimable
Subtotal (95% CI)		**2882**		**2871**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.3.6 Vulvar cancer: Cervarix (females, age 15-25; follow-up until 48 months)						
HPV-008: Cervarix vs. Havrix (f, 15-25; 48)	0	9319	0	9325		Not estimable
Subtotal (95% CI)		**9319**		**9325**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.3.7 Vulvar cancer: Gardasil (females, age 15-26; follow-up until 45 months)						
V501-013: Gardasil vs. AAHS (f, 16-24; 45)	0	2723	0	2732		Not estimable
Subtotal (95% CI)		**2723**		**2732**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**24510**		**24486**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



*2.3. Risk ratio for 'medically significant conditions' (GlaxoSmithKline): not applicable; risk ratio for 'new medical history' (Merck Sharp & Dohme): not applicable.

2.4. Incidence of HPV-related carcinoma in situ (anal intraepithelial neoplasia grade 3 [AIN3], cervical adenocarcinoma in situ [AIS], cervical intraepithelial neoplasia grade 3 [CIN3], penile intraepithelial neoplasia grade 3 [PIN3], vaginal intraepithelial neoplasia grade 3 [VIN3] and vulvar intraepithelial neoplasia grade 3 [VaIN3]) irrespective of HPV type: intention to treat analysis

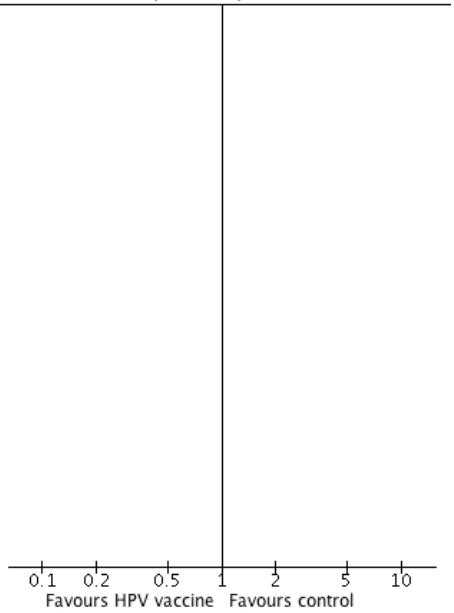
Study or Subgroup	HPV vaccine Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
2.4.1 AIS: Cervarix (females, age 15-25; follow-up until 48 months)						
HPV-008: Cervarix vs. Havrix (f, 15-25; 48)	0	9319	0	9325		Not estimable
Subtotal (95% CI)		**9319**		**9325**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.4.2 AIS: Gardasil (females, age 15-26; follow-up until 45 months)						
V501-013: Gardasil vs. AAHS (f, 16-24; 45)	0	2723	0	2732		Not estimable
V501-015: Gardasil vs. AAHS (f, 15-26; 36)	0	6087	0	6080		Not estimable
Subtotal (95% CI)		**8810**		**8812**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.4.3 AIS: Gardasil (females, age 21-46; follow-up until 48 months)						
V501-019: Gardasil vs. AAHS (f, 21-46; 48)	0	1911	0	1908		Not estimable
Subtotal (95% CI)		**1911**		**1908**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.4.4 CIN3: Cervarix (females, age 15-25; follow-up until 48 months)						
HPV-008: Cervarix vs. Havrix (f, 15-25; 48)	0	9319	0	9325		Not estimable
Subtotal (95% CI)		**9319**		**9325**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.4.5 CIN3: Gardasil (females, age 15-26; follow-up until 45 months)						
V501-013: Gardasil vs. AAHS (f, 16-24; 45)	0	2723	0	2732		Not estimable
V501-015: Gardasil vs. AAHS (f, 15-26; 36)	0	6087	0	6080		Not estimable
Subtotal (95% CI)		**8810**		**8812**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.4.6 CIN3: Gardasil (females, age 21-46; follow-up until 48 months)						
V501-019: Gardasil vs. AAHS (f, 21-46; 48)	0	1911	0	1908		Not estimable
Subtotal (95% CI)		**1911**		**1908**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**40080**		**40090**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



*2.4. Risk ratio for 'medically significant conditions' (GlaxoSmithKline): not applicable; risk ratio for 'new medical history' (Merck Sharp & Dohme): not applicable.

2.5. Incidence of HPV-related moderate intraepithelial neoplasia (anal intraepithelial neoplasia grade 2 [AIN2], cervical intraepithelial neoplasia grade 2 [CIN2], penile intraepithelial neoplasia grade 2 [PIN2], vaginal intraepithelial neoplasia grade 2 [VIN2] and vulvar intraepithelial neoplasia grade 2 [VaIN2]) irrespective of HPV type: intention to treat analysis

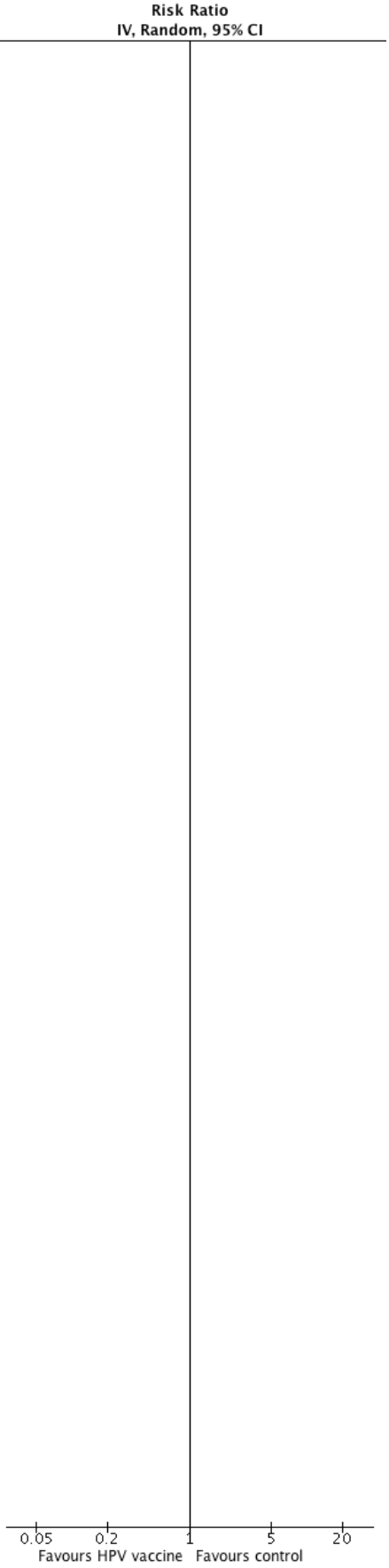
Study or Subgroup	HPV vaccine Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
2.5.1 CIN2: Cervarix (females, age 15–25; follow-up until 48 months)						
HPV-008: Cervarix vs. Havrix (f, 15–25; 48)	0	9319	0	9325		Not estimable
Subtotal (95% CI)		**9319**		**9325**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.5.2 CIN2: Gardasil (females, age 15–26; follow-up until 45 months)						
V501-013: Gardasil vs. AAHS (f, 16–24; 45)	0	2723	0	2732		Not estimable
V501-015: Gardasil vs. AAHS (f, 15–26; 36)	0	6087	0	6080		Not estimable
Subtotal (95% CI)		**8810**		**8812**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.5.3 CIN2: Gardasil (females, age 21–46; follow-up until 48 months)						
V501-019: Gardasil vs. AAHS (f, 21–46; 48)	0	1911	0	1908		Not estimable
Subtotal (95% CI)		**1911**		**1908**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**20040**		**20045**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



*2.5. Risk ratio for 'medically significant conditions' (GlaxoSmithKline): not applicable; risk ratio for 'new medical history' (Merck Sharp & Dohme): not applicable.

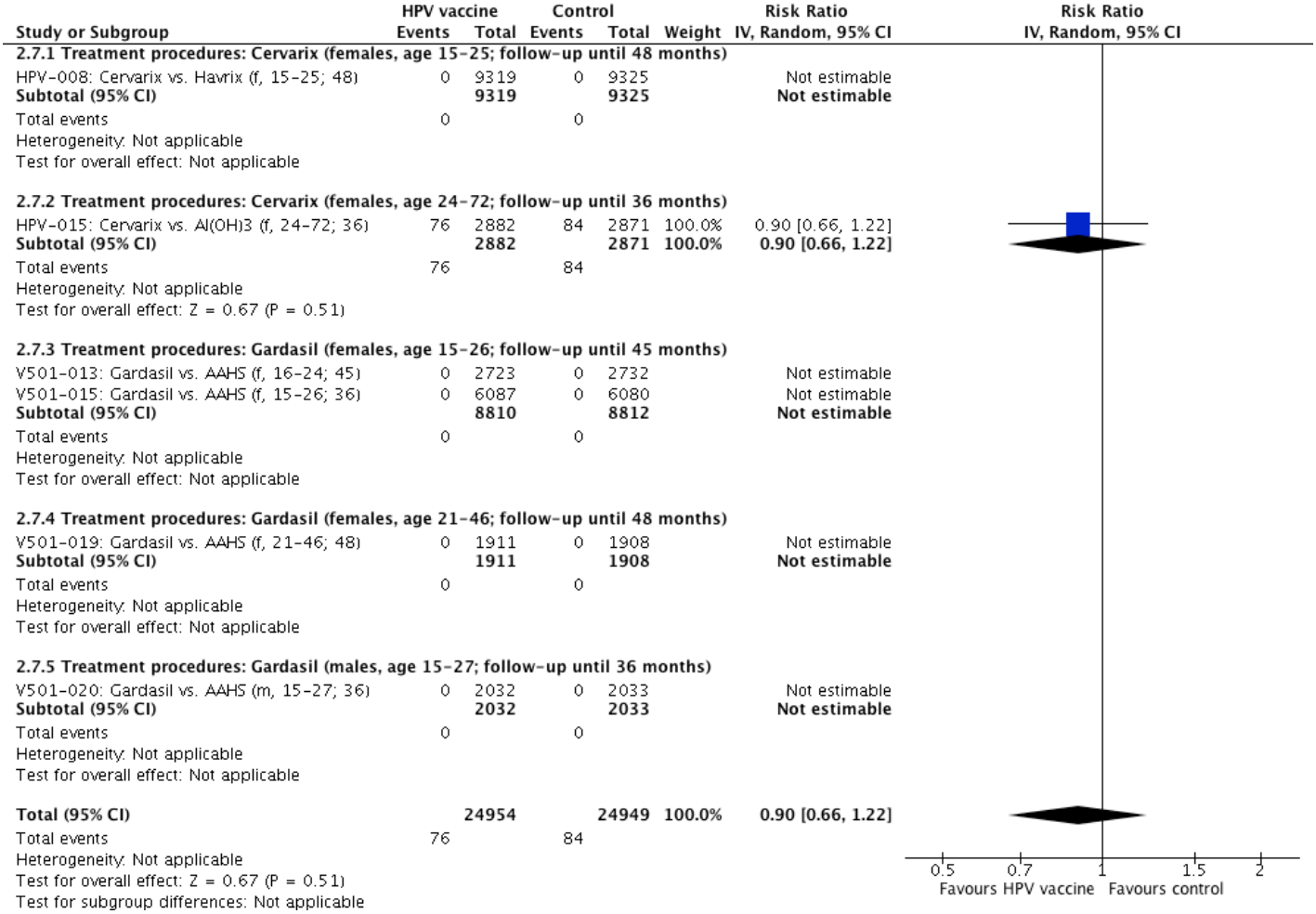
2.6. Incidence of HPV-related moderate intraepithelial neoplasia or worse (AIN2$^+$, CIN2$^+$, PIN2$^+$, VIN2$^+$, VaIN2$^+$) irrespective of HPV type: intention to treat analysis

Study or Subgroup	HPV vaccine Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
2.6.1 CIN2+: Cervarix (females, age 15-25; follow-up until 48 months)						
HPV-008: Cervarix vs. Havrix (f, 15-25; 48)	0	9319	0	9325		Not estimable
Subtotal (95% CI)		**9319**		**9325**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.6.2 CIN2+: Cervarix (females, age 22-29; follow-up until 12 months)						
HPV-063: Cervarix vs. Aimmugen (f, 22-29; 12)	0	464	0	463		Not estimable
Subtotal (95% CI)		**464**		**463**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.6.3 CIN2+: Cervarix (females, age 24-72; follow-up until 36 months)						
HPV-015: Cervarix vs. Al(OH)3 (f, 24-72; 36)	0	2882	0	2871		Not estimable
Subtotal (95% CI)		**2882**		**2871**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.6.4 CIN2+: Gardasil (females, age 15-26; follow-up until 45 months)						
V501-013: Gardasil vs. AAHS (f, 16-24; 45)	0	2723	0	2732		Not estimable
V501-015: Gardasil vs. AAHS (f, 15-26; 36)	0	6087	0	6080		Not estimable
Subtotal (95% CI)		**8810**		**8812**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.6.5 CIN2+: Gardasil (females, age 21-46; follow-up until 48 months)						
V501-019: Gardasil vs. AAHS (f, 21-46; 48)	0	1911	0	1908		Not estimable
Subtotal (95% CI)		**1911**		**1908**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.6.6 PIN2+: Gardasil (males, age 15-27; follow-up until 36 months)						
V501-020: Gardasil vs. AAHS (m, 15-27; 36)	0	2032	0	2033		Not estimable
Subtotal (95% CI)		**2032**		**2033**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.6.7 VIN2+: Gardasil (females, age 15-26; follow-up until 45 months)						
V501-013: Gardasil vs. AAHS (f, 16-24; 45)	0	2723	0	2732		Not estimable
V501-015: Gardasil vs. AAHS (f, 15-26; 36)	0	6087	0	6080		Not estimable
Subtotal (95% CI)		**8810**		**8812**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.6.8 VaIN2+: Gardasil (females, age 15-26; follow-up until 45 months)						
V501-013: Gardasil vs. AAHS (f, 16-24; 45)	0	2723	0	2732		Not estimable
V501-015: Gardasil vs. AAHS (f, 15-26; 36)	0	6087	0	6080		Not estimable
Subtotal (95% CI)		**8810**		**8812**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.6.9 VaIN2+: Gardasil (females, age 21-46; follow-up until 48 months)						
V501-019: Gardasil vs. AAHS (f, 21-46; 48)	0	1911	0	1908		Not estimable
Subtotal (95% CI)		**1911**		**1908**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.6.10 VIN2+ or VaIN2+: Cervarix (females, age 15-25; follow-up until 48 months)						
HPV-008: Cervarix vs. Havrix (f, 15-25; 48)	0	9319	0	9325		Not estimable
Subtotal (95% CI)		**9319**		**9325**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**54268**		**54269**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



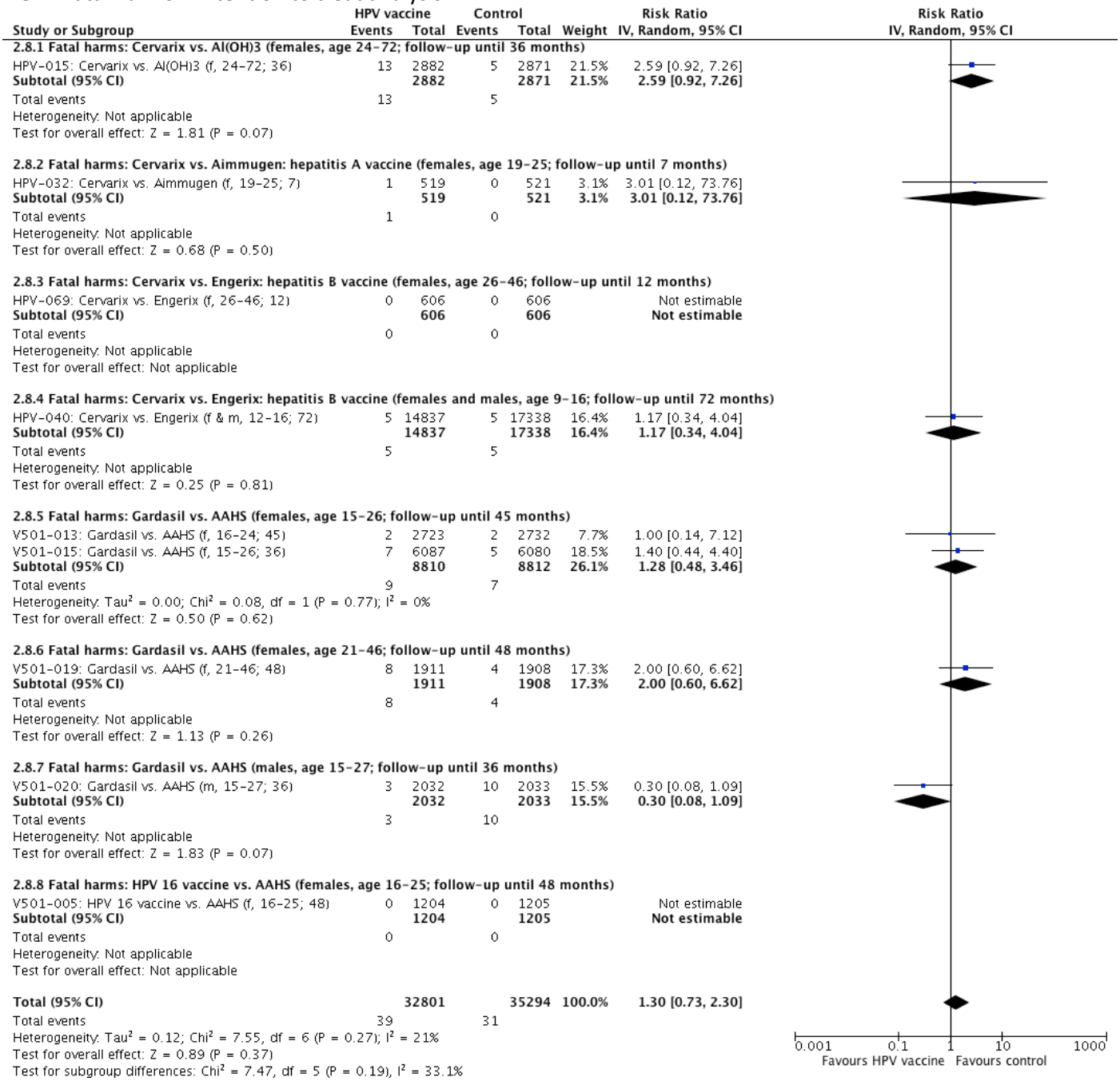
*2.6. Risk ratio for 'medically significant conditions' (GlaxoSmithKline): not applicable; risk ratio for 'new medical history' (Merck Sharp & Dohme): not applicable.

2.7. Number of treatment procedures (both surgical and non-surgical treatment) due to HPV-related diseases irrespective of HPV type: intention to treat analysis



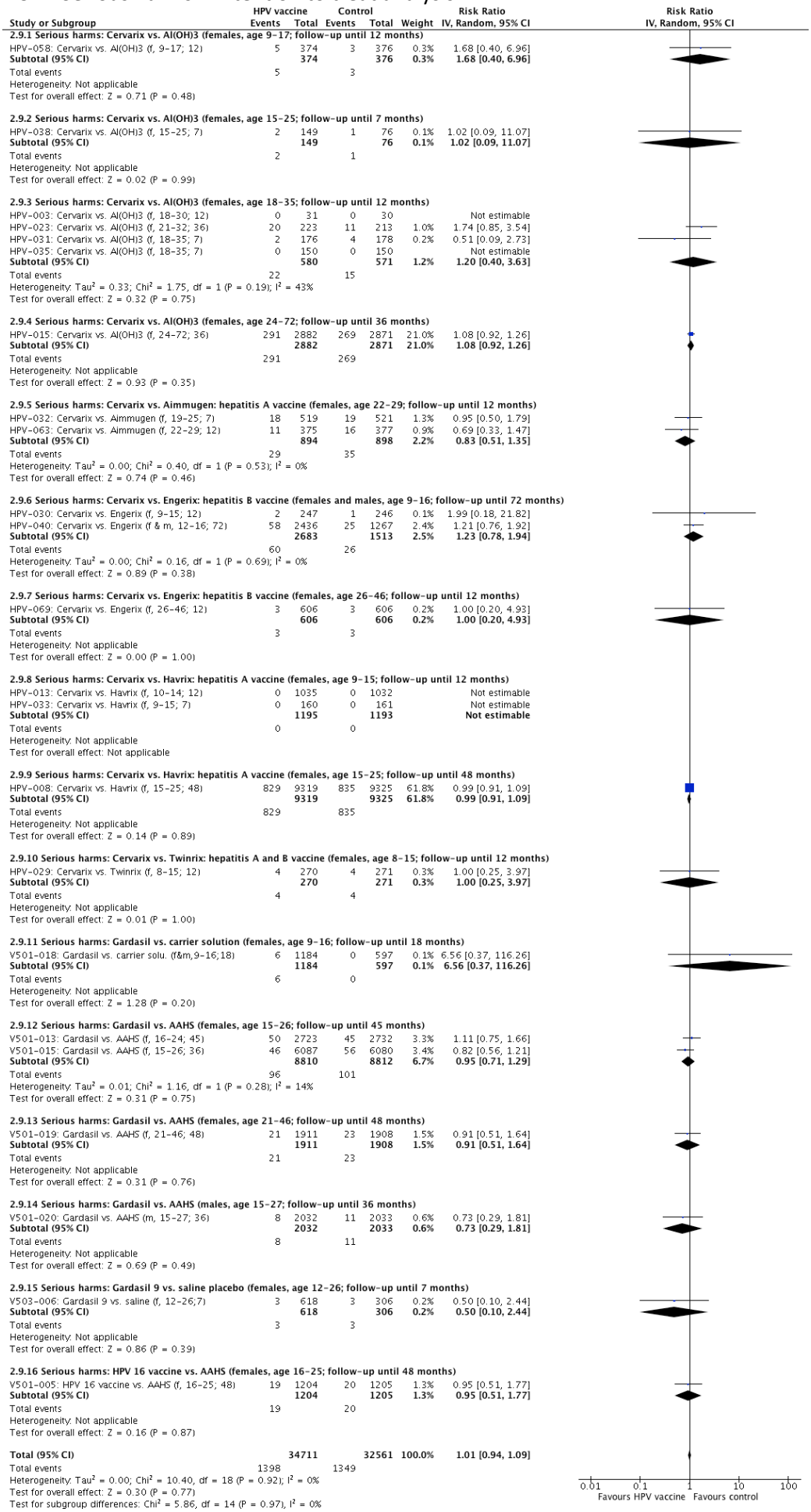
*2.7. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 0.90 [0.66, 1.22]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): not applicable.

2.8. Fatal harms*: intention to treat analysis



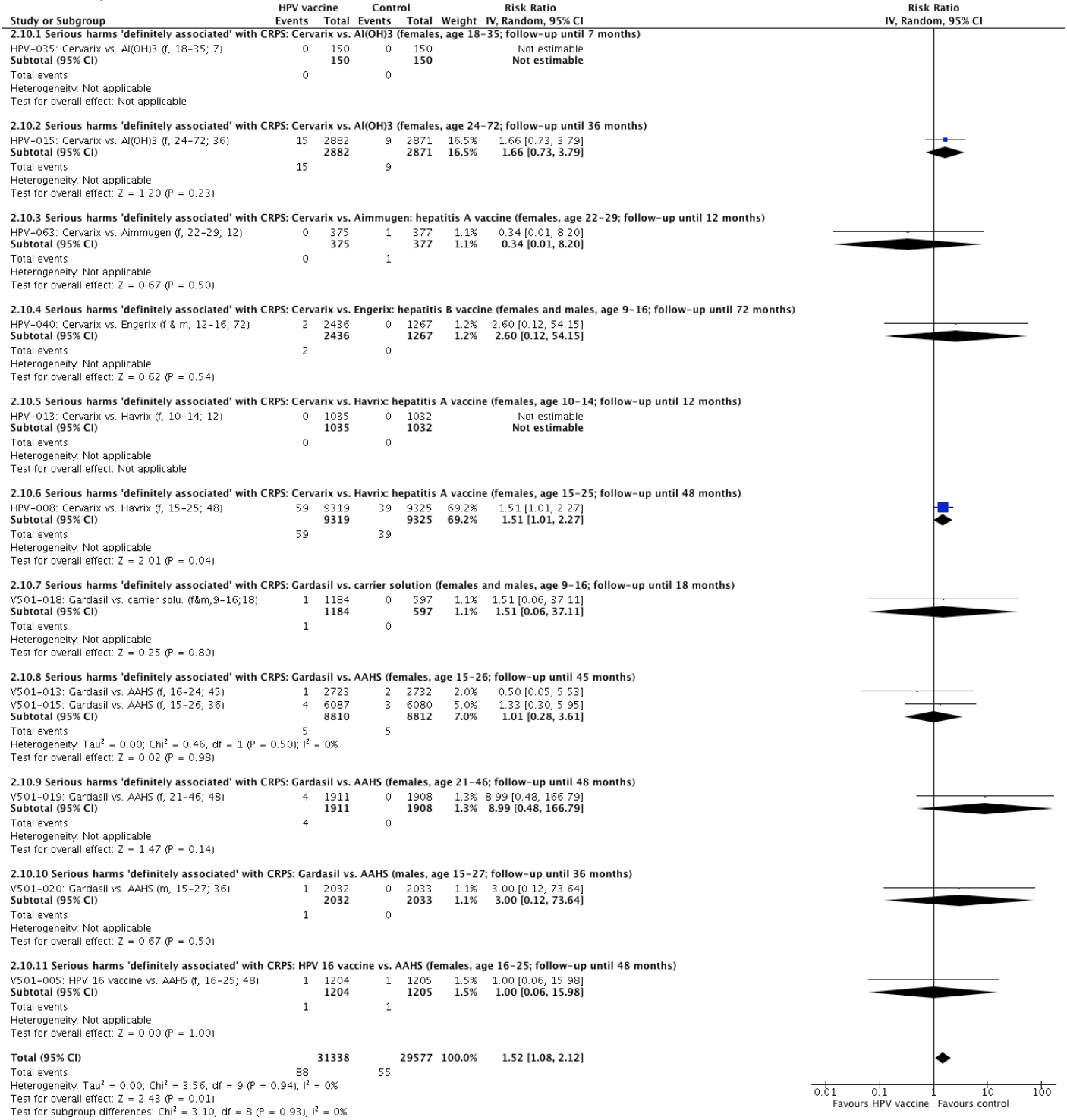
*2.8. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 1.92 [0.89, 4.15]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 0.98 [0.41, 2.33].

2.9. Serious harms*: intention to treat analysis



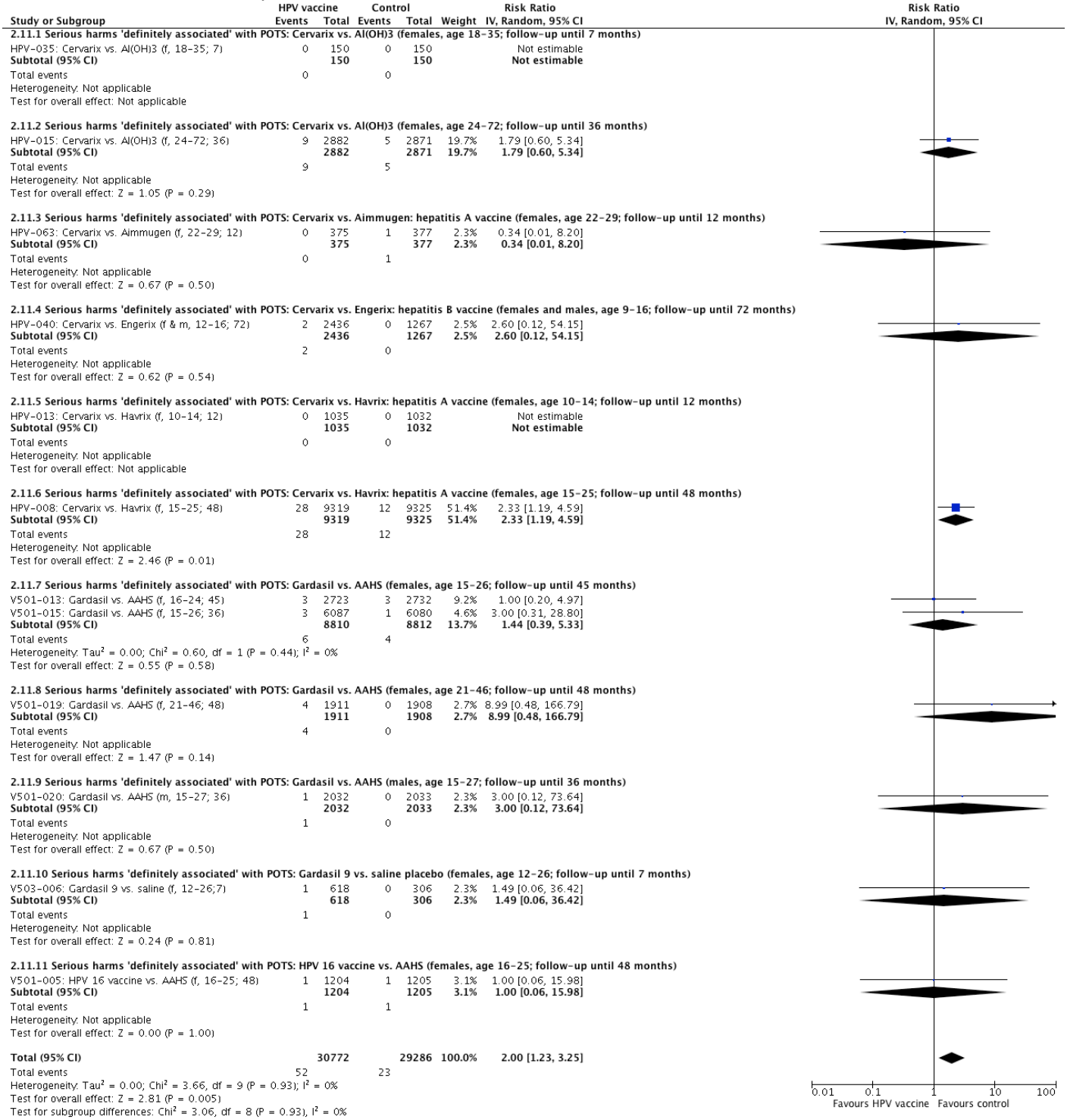
*2.9. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 1.02 [0.95, 1.10]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 0.93 [0.74, 1.16].

2.10. Serious harms judged as 'definitely associated'* with chronic regional pain syndrome (CRPS): intention to treat analysis



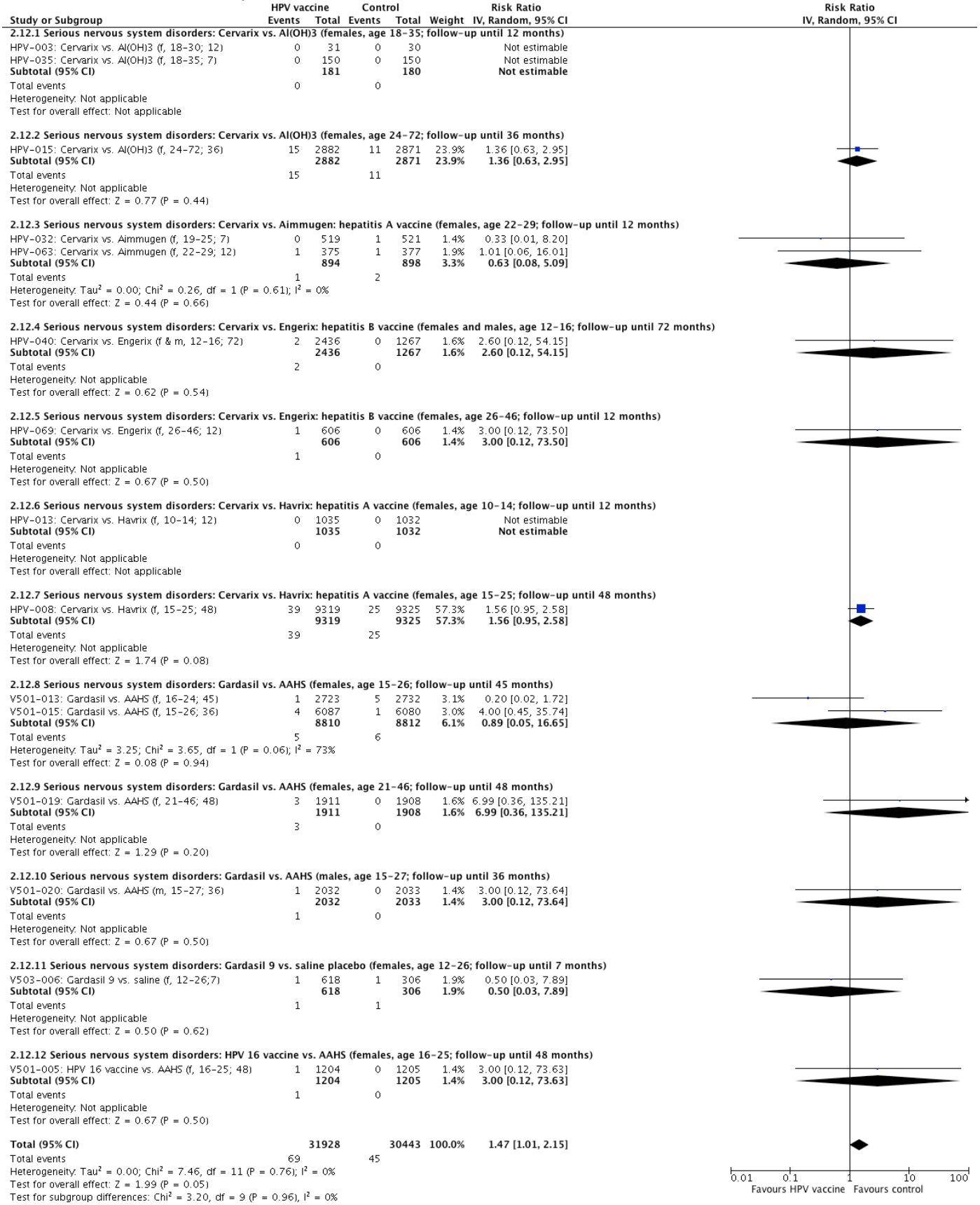
*2.10. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): **1.52 [1.07, 2.18]**; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 1.48 [0.56, 3.89]. We asked a physician with clinical expertise in CRPS to assess the reported MedDRA preferred terms as 'definitely,' 'probably,' 'probably not' or 'definitely not' associated with CRPS. We sent an Excel sheet to the physician with all the reported MedDRA terms. The physician was blinded, as the Excel sheet contained no outcome data. When the physician had assessed all the MedDRA terms, we synthesized the data for those MedDRA terms that the physician judged 'definitely' associated with CRPS and compared it to the reported serious harms.

2.11. Serious harms judged as 'definitely associated'* with postural orthostatic tachycardia syndrome (POTS): intention to treat analysis



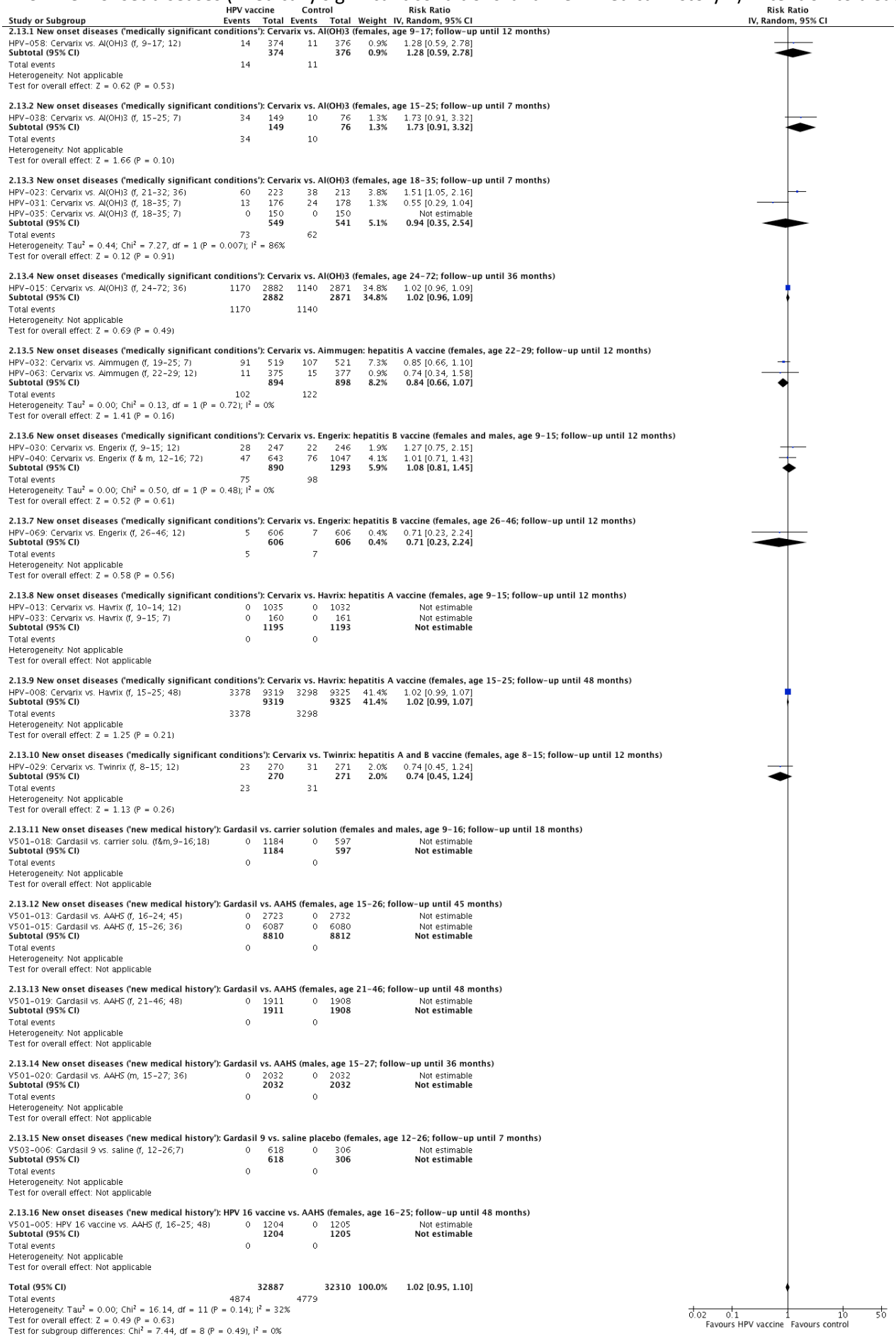
*2.11. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): **2.06 [1.18, 3.60]**; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 1.83 [0.68, 4.89]. We asked a physician with clinical expertise in POTS to assess the reported MedDRA preferred terms as 'definitely,' 'probably,' 'probably not' or 'definitely not' associated with POTS. We sent an Excel sheet to the physician with all the reported MedDRA terms. The physician was blinded, as the Excel sheet contained no outcome data. When the physician had assessed all the MedDRA terms, we synthesized the data for those MedDRA terms that the physician judged 'definitely' associated with POTS and compared it to the reported serious harms.

2.12. Serious harms reported within the MedDRA system organ class 'nervous system disorders (10029205)'*: intention to treat analysis



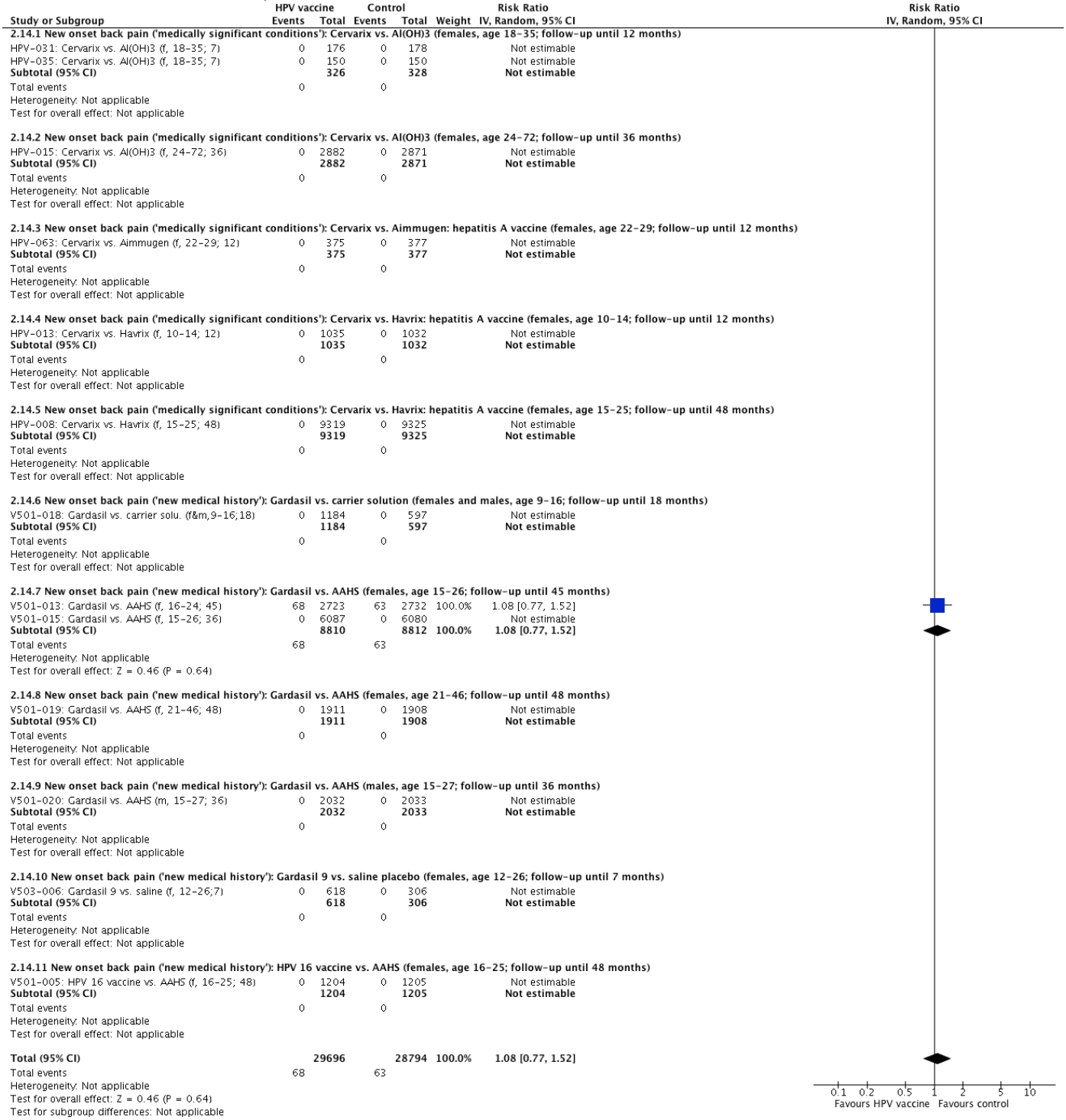
*2.12. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 1.48 [0.99, 2.22]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 1.45 [0.43, 4.82].

2.13. New onset diseases ('medically significant conditions' and 'new medical history'*): intention to treat analysis



*2.13. Risk ratio for 'medically significant conditions' (GlaxoSmithKline): 1.02 [0.95, 1.10]; risk ratio for 'new medical history' (Merck Sharp & Dohme): not applicable.

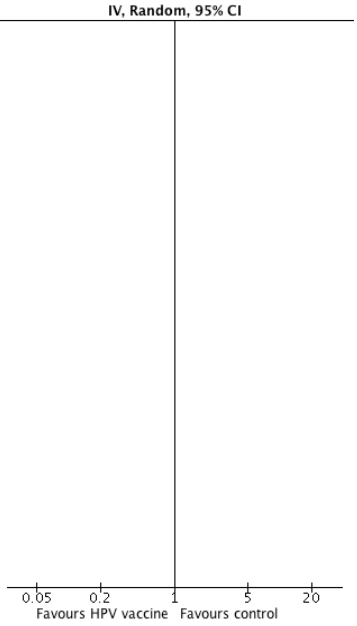
2.14. New onset diseases most associated with the HPV vaccines ('medically significant conditions'*) - 'back pain': intention to treat analysis



*2.14. Risk ratio for 'medically significant conditions' (GlaxoSmithKline): not applicable; risk ratio for 'new medical history' (Merck Sharp & Dohme): 1.08 [0.77, 1.52].

2.15. New onset diseases most inversely associated with the HPV vaccines ('new medical history') - 'vaginal infection': intention to treat analysis

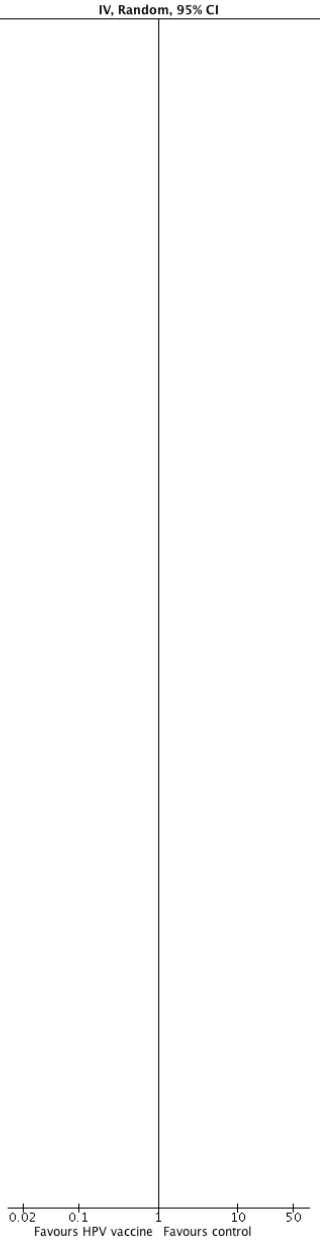
Study or Subgroup	HPV vaccine Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
2.15.1 New onset vaginal infection ('new medical history'): Gardasil vs. carrier solution (females and males, age 9-16; follow-up until 18 months)						
V501-018: Gardasil vs. carrier solu. (f&m,9-16;18)	0	1184	0	597		Not estimable
Subtotal (95% CI)		**1184**		**597**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.15.2 New onset vaginal infection ('new medical history'): Gardasil vs. AAHS (females, age 15-26; follow-up until 45 months)						
V501-013: Gardasil vs. AAHS (f, 16-24; 45)	0	2723	0	2732		Not estimable
V501-015: Gardasil vs. AAHS (f, 15-26; 36)	0	6087	0	6080		Not estimable
Subtotal (95% CI)		**8810**		**8812**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.15.3 New onset vaginal infection ('new medical history'): Gardasil vs. AAHS (females, age 21-46; follow-up until 48 months)						
V501-019: Gardasil vs. AAHS (f, 21-46; 48)	0	1911	0	1908		Not estimable
Subtotal (95% CI)		**1911**		**1908**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.15.4 New onset vaginal infection ('new medical history'): Gardasil 9 vs. saline placebo (females, age 12-26; follow-up until 7 months)						
V503-006: Gardasil 9 vs. saline (f, 12-26;7)	0	618	0	306		Not estimable
Subtotal (95% CI)		**618**		**306**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**12523**		**11623**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



*2.15. Risk ratio for 'medically significant conditions' (GlaxoSmithKline): not applicable; risk ratio for 'new medical history' (Merck Sharp & Dohme): not applicable.

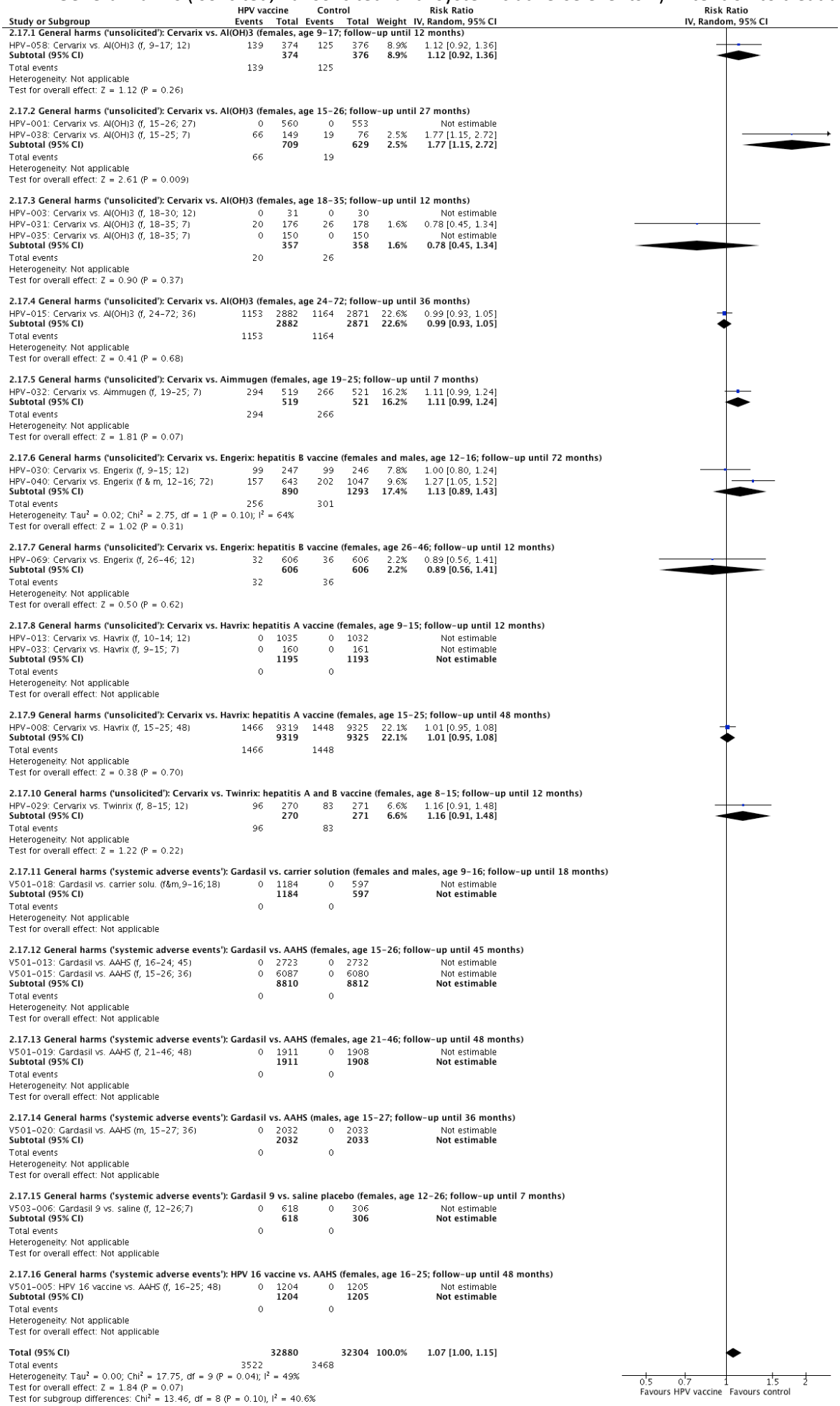
2.16. New onset diseases ('medically significant conditions' and 'new medical history') reported within the MedDRA system organ class 'vascular disorders (10047065)': intention to treat analysis

Study or Subgroup	HPV vaccine Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
2.16.1 New onset vascular disorders ('medically significant conditions'): Cervarix vs. Al(OH)3 (females, age 24-72; follow-up until 36 months)						
HPV-015: Cervarix vs. Al(OH)3 (f, 24-72; 36)	0	2882	0	2871		Not estimable
Subtotal (95% CI)		**2882**		**2871**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.16.2 New onset vascular disorders ('medically significant conditions'): Cervarix vs. Aimmugen: hepatitis A vaccine (females, age 22-29; follow-up until 12 months)						
HPV-063: Cervarix vs. Aimmugen (f, 22-29; 12)	0	375	0	377		Not estimable
Subtotal (95% CI)		**375**		**377**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.16.3 New onset vascular disorders ('medically significant conditions'): Cervarix vs. Havrix: hepatitis A vaccine (females, age 10-14; follow-up until 12 months)						
HPV-013: Cervarix vs. Havrix (f, 10-14; 12)	0	1035	0	1032		Not estimable
Subtotal (95% CI)		**1035**		**1032**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.16.4 New onset vascular disorders ('medically significant conditions'): Cervarix vs. Havrix: hepatitis A vaccine (females, age 15-25; follow-up until 48 months)						
HPV-008: Cervarix vs. Havrix (f, 15-25; 48)	0	9319	0	9325		Not estimable
Subtotal (95% CI)		**9319**		**9325**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.16.5 New onset vascular disorders ('medically significant conditions'): Cervarix vs. Twinrix: hepatitis A and B vaccine (females, age 8-15; follow-up until 12 months)						
HPV-029: Cervarix vs. Twinrix (f, 8-15; 12)	0	270	0	271		Not estimable
Subtotal (95% CI)		**270**		**271**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.16.6 New onset vascular disorders ('new medical history'): Gardasil vs. carrier solution (females and males, age 9-16; follow-up until 18 months)						
V501-018: Gardasil vs. carrier solu. (f&m,9-16;18)	0	1184	0	597		Not estimable
Subtotal (95% CI)		**1184**		**597**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.16.7 New onset vascular disorders ('new medical history'): Gardasil vs. AAHS (females, age 15-26; follow-up until 45 months)						
V501-013: Gardasil vs. AAHS (f, 16-24; 45)	0	2723	0	2732		Not estimable
V501-015: Gardasil vs. AAHS (f, 15-26; 36)	0	6087	0	6080		Not estimable
Subtotal (95% CI)		**8810**		**8812**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.16.8 New onset vascular disorders ('new medical history'): Gardasil vs. AAHS (females, age 21-46; follow-up until 48 months)						
V501-019: Gardasil vs. AAHS (f, 21-46; 48)	0	1911	0	1908		Not estimable
Subtotal (95% CI)		**1911**		**1908**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.16.9 New onset vascular disorders ('new medical history'): Gardasil vs. AAHS (males, age 15-27; follow-up until 36 months)						
V501-020: Gardasil vs. AAHS (m, 15-27; 36)	0	2032	0	2033		Not estimable
Subtotal (95% CI)		**2032**		**2033**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.16.10 New onset vascular disorders ('new medical history'): HPV 16 vaccine vs. AAHS (females, age 16-25; follow-up until 48 months)						
V501-005: HPV 16 vaccine vs. AAHS (f, 16-25; 48)	0	1204	0	1205		Not estimable
Subtotal (95% CI)		**1204**		**1205**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**29022**		**28431**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



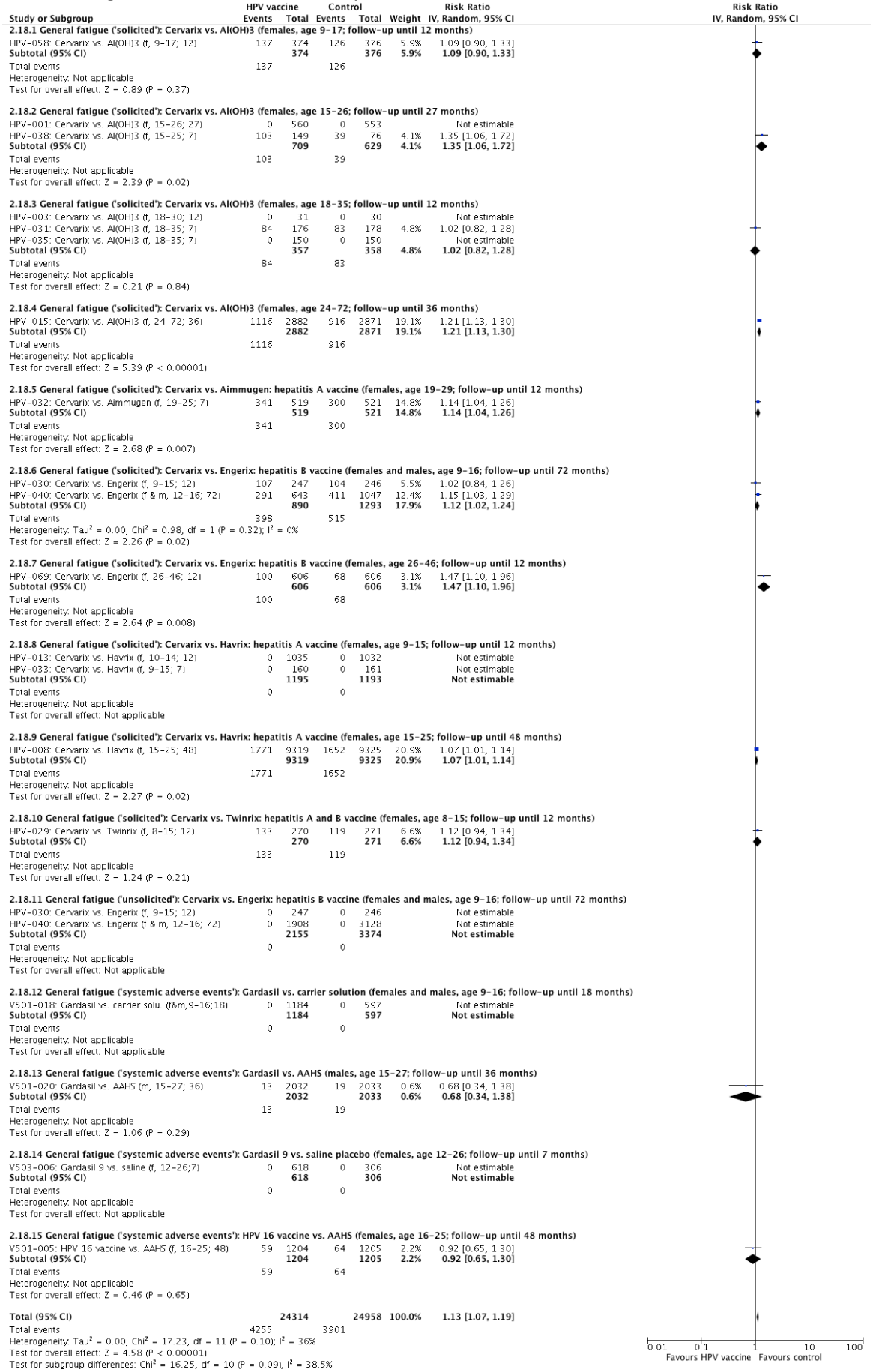
*2.16. Risk ratio for 'medically significant conditions' (GlaxoSmithKline): not applicable; risk ratio for 'new medical history' (Merck Sharp & Dohme): not applicable.

2.17. General harms ('solicited,' 'unsolicited' and 'systemic adverse events'*): intention to treat analysis



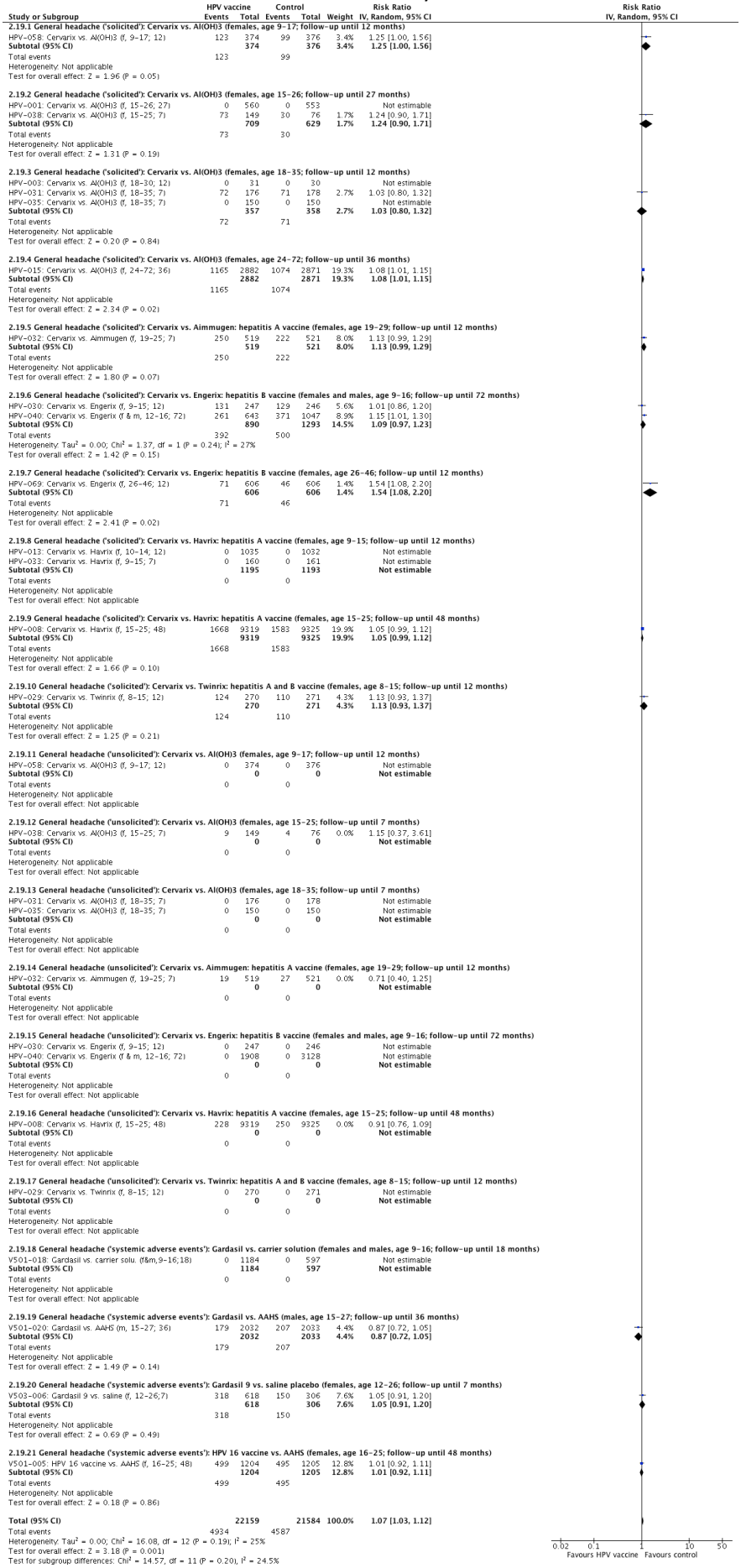
*2.17. Risk ratio for 'solicited' (GlaxoSmithKline): **1.07 [1.00, 1.15]**; risk ratio for 'systemic adverse events' (Merck Sharp & Dohme): not applicable.

2.18. General harms most associated with the HPV vaccines ('solicited,' 'unsolicited' and 'systemic adverse events'*) - 'fatigue': intention to treat analysis



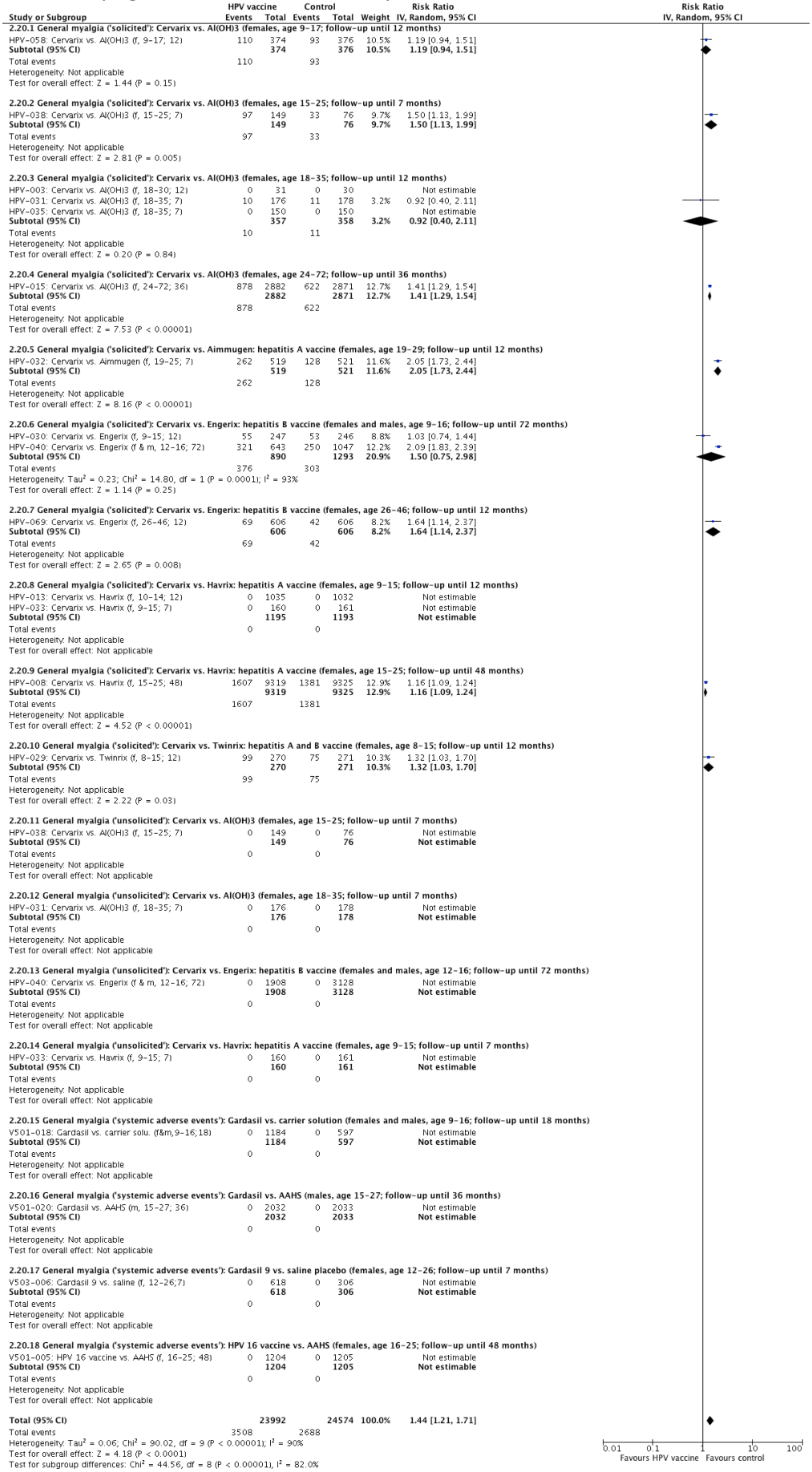
*2.18. Risk ratio for 'solicited' (GlaxoSmithKline): **1.14 [1.08, 1.20]**; risk ratio for 'unsolicited' (GlaxoSmithKline): not applicable; risk ratio for 'systemic adverse events' (Merck Sharp & Dohme): 0.87 [0.64, 1.19]. To avoid double counting of participants in the total risk ratio estimate, we excluded the 'unsolicited' adverse events from total risk ratio estimate for studies that reported 'solicited' adverse events.

2.19. General harms most associated with the HPV vaccines ('solicited,' 'unsolicited' and 'systemic adverse events'*) - 'headache': intention to treat analysis



*2.19. Risk ratio for 'solicited' (GlaxoSmithKline): **1.09 [1.05, 1.13]**; risk ratio for 'unsolicited' (GlaxoSmithKline): 0.90 [0.76, 1.06]; risk ratio for 'systemic adverse events' (Merck Sharp & Dohme): 0.99 [0.91, 1.09]. To avoid double counting of participants in the total risk ratio estimate, we excluded the 'unsolicited' adverse events from total risk ratio estimate for studies that reported 'solicited' adverse events.

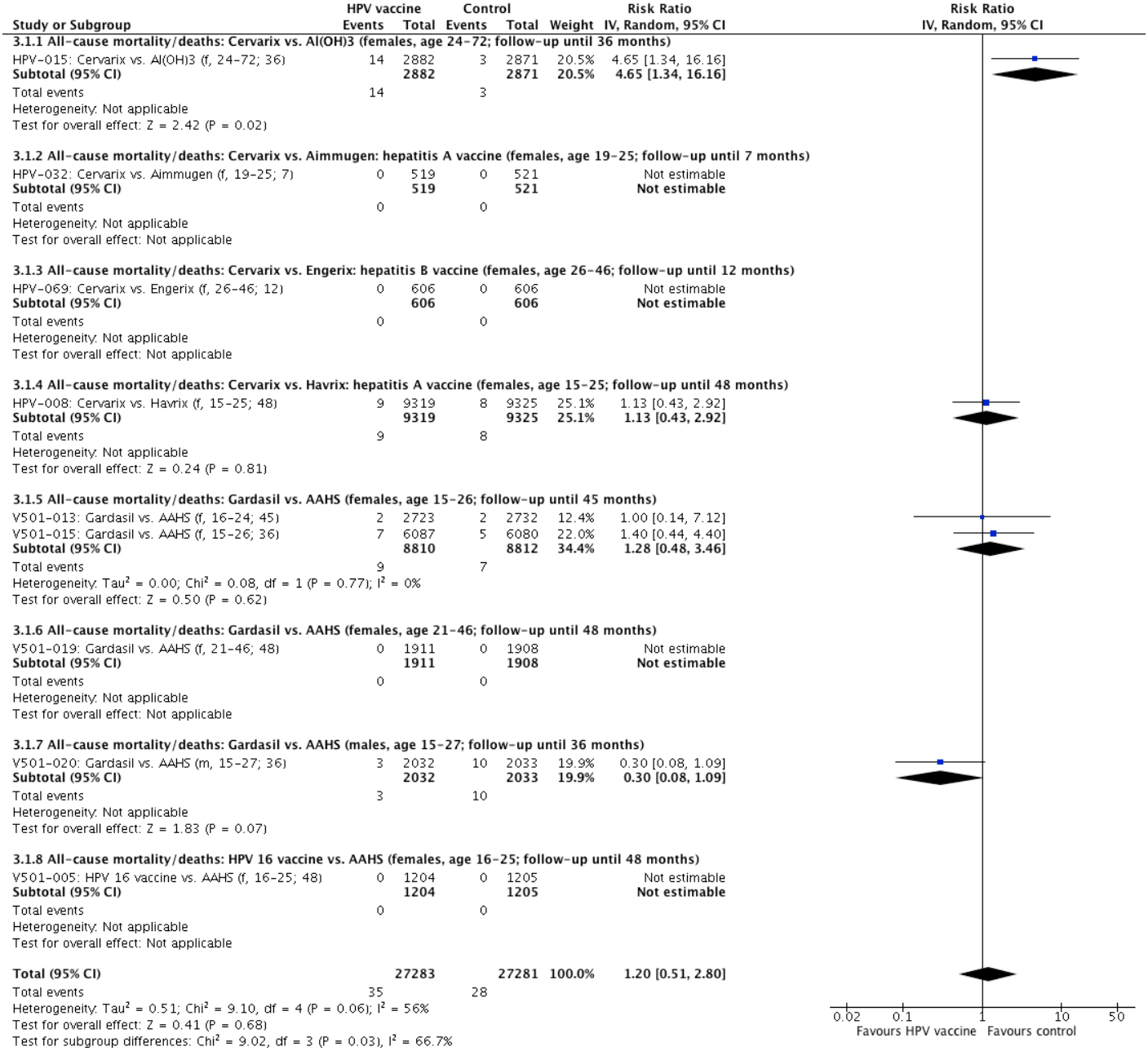
2.20. General harms most associated with the HPV vaccines ('solicited,' 'unsolicited' and 'systemic adverse events'*) - 'myalgia': intention to treat analysis



*2.20. Risk ratio for 'solicited' (GlaxoSmithKline): **1.37 [1.31, 1.43]**; risk ratio for 'unsolicited' (GlaxoSmithKline): not applicable; risk ratio for 'systemic adverse events' (Merck Sharp & Dohme): not applicable. To avoid double counting of participants in the total risk ratio estimate, we excluded the 'unsolicited' adverse events from total risk ratio estimate for studies that reported 'solicited' adverse events.

3. Journal publications

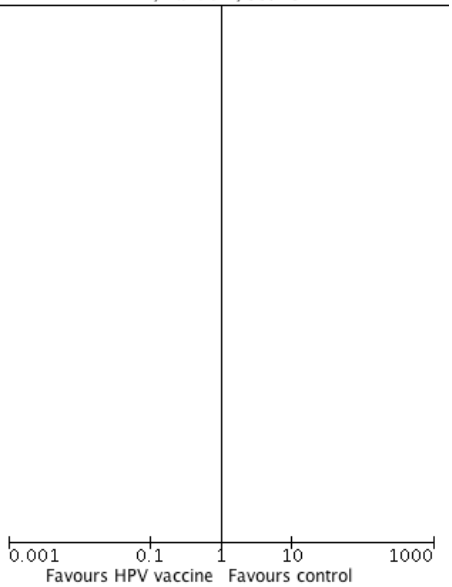
3.1. All-cause mortality/deaths*: intention to treat analysis



*3.1. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 2.16 [0.54, 8.61]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 0.74 [0.27, 2.05].

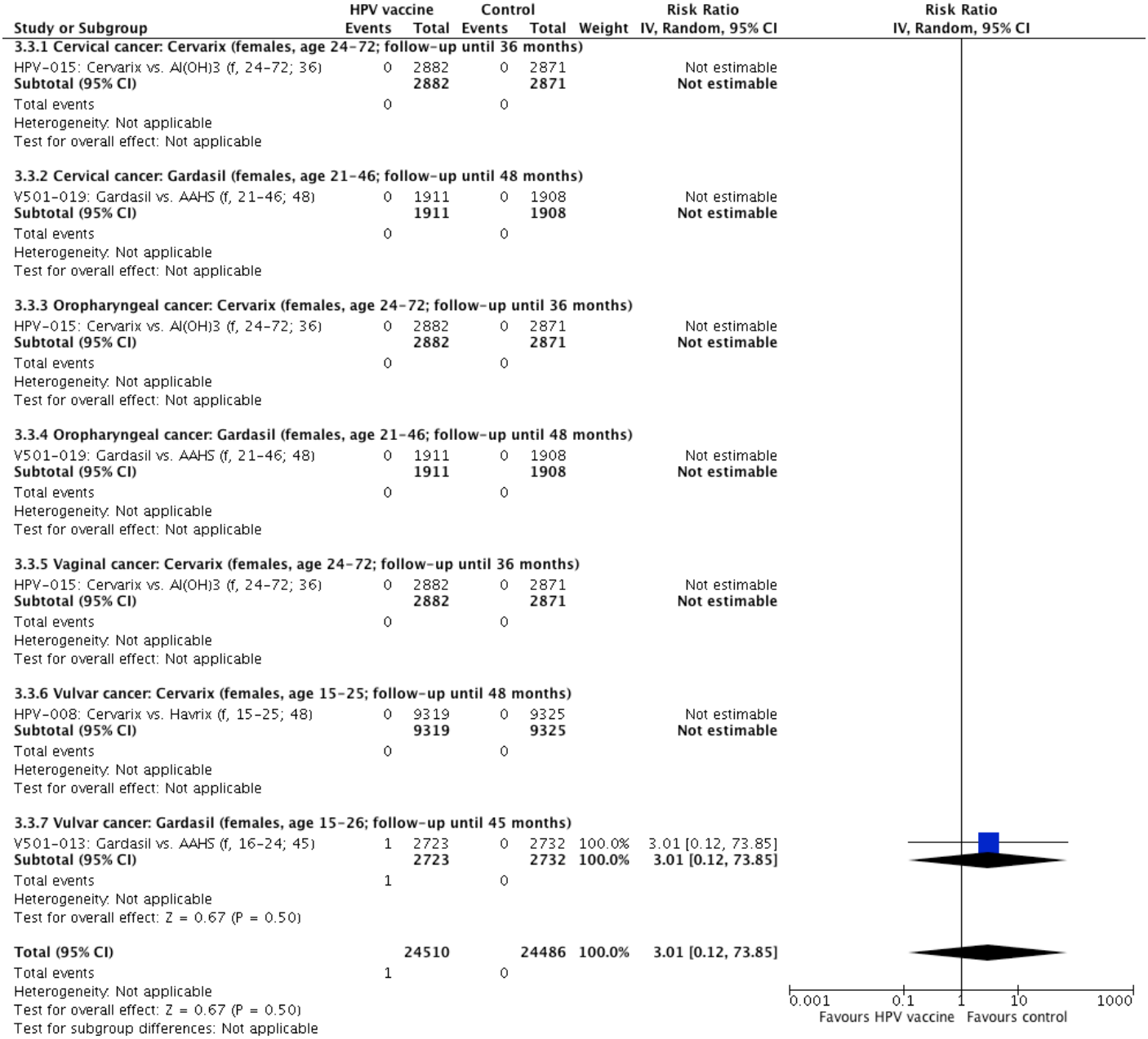
3.2. Mortality/deaths from HPV-related cancers (anal, cervical, oropharyngeal, penile, vaginal and vulvar) irrespective of HPV type: intention to treat analysis

Study or Subgroup	HPV vaccine Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
3.2.1 Cervical cancer: Cervarix (females, age 24-72; follow-up until 36 months)						
HPV-015: Cervarix vs. Al(OH)3 (f, 24-72; 36)	0	2882	0	2871		Not estimable
Subtotal (95% CI)		**2882**		**2871**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.2.2 Oropharyngeal cancer: Cervarix (females, age 24-72; follow-up until 36 months)						
HPV-015: Cervarix vs. Al(OH)3 (f, 24-72; 36)	0	2882	0	2871		Not estimable
Subtotal (95% CI)		**2882**		**2871**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.2.3 Oropharyngeal cancer: Gardasil (females, age 21-46; follow-up until 48 months)						
V501-019: Gardasil vs. AAHS (f, 21-46; 48)	0	1911	0	1908		Not estimable
Subtotal (95% CI)		**1911**		**1908**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**7675**		**7650**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



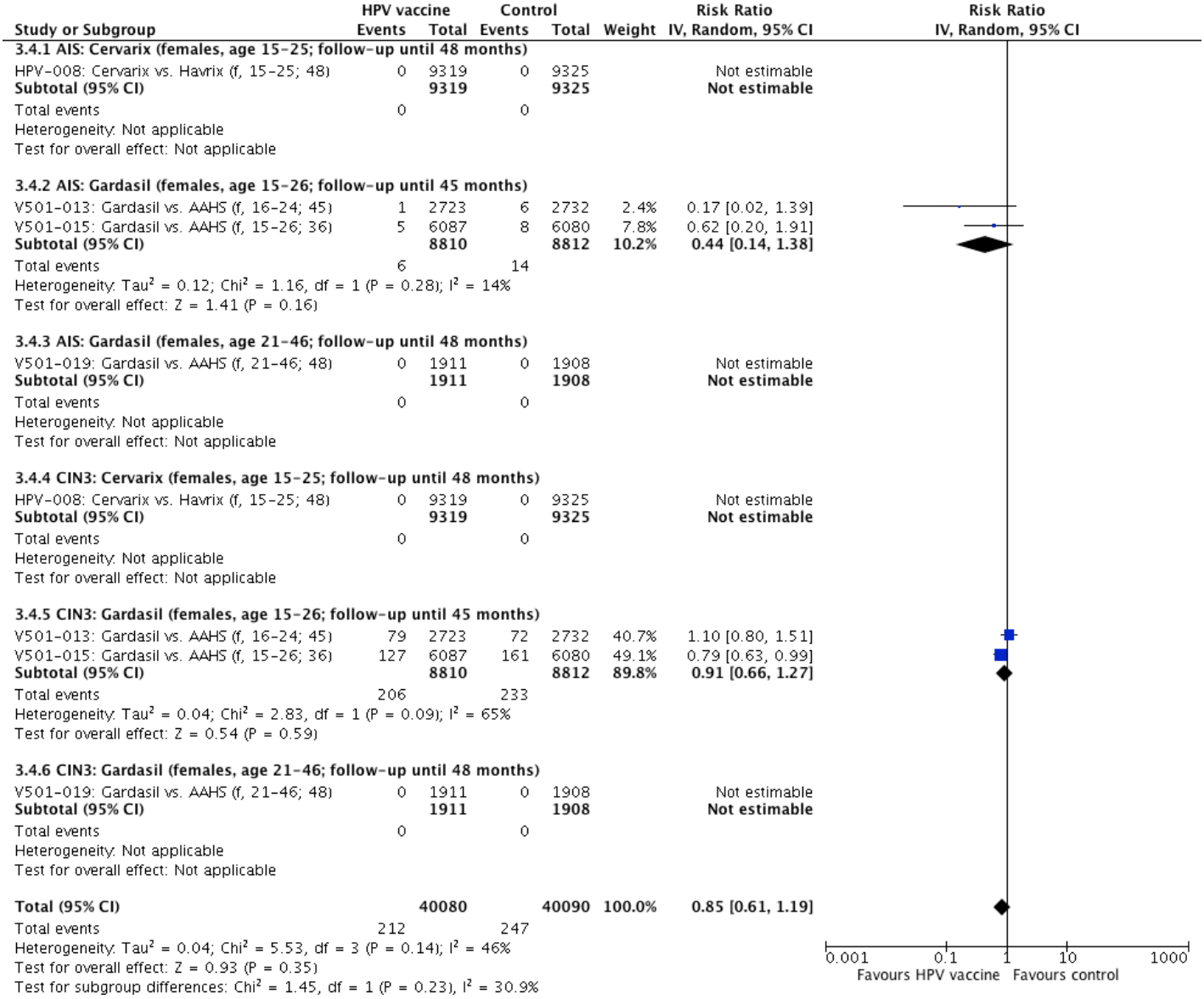
*3.2. Risk ratio for 'medically significant conditions' (GlaxoSmithKline): not applicable; risk ratio for 'new medical history' (Merck Sharp & Dohme): not applicable.

3.3. Incidence of HPV-related cancers (anal, cervical, oropharyngeal, penile, vaginal and vulvar) irrespective of HPV type*: intention to treat analysis



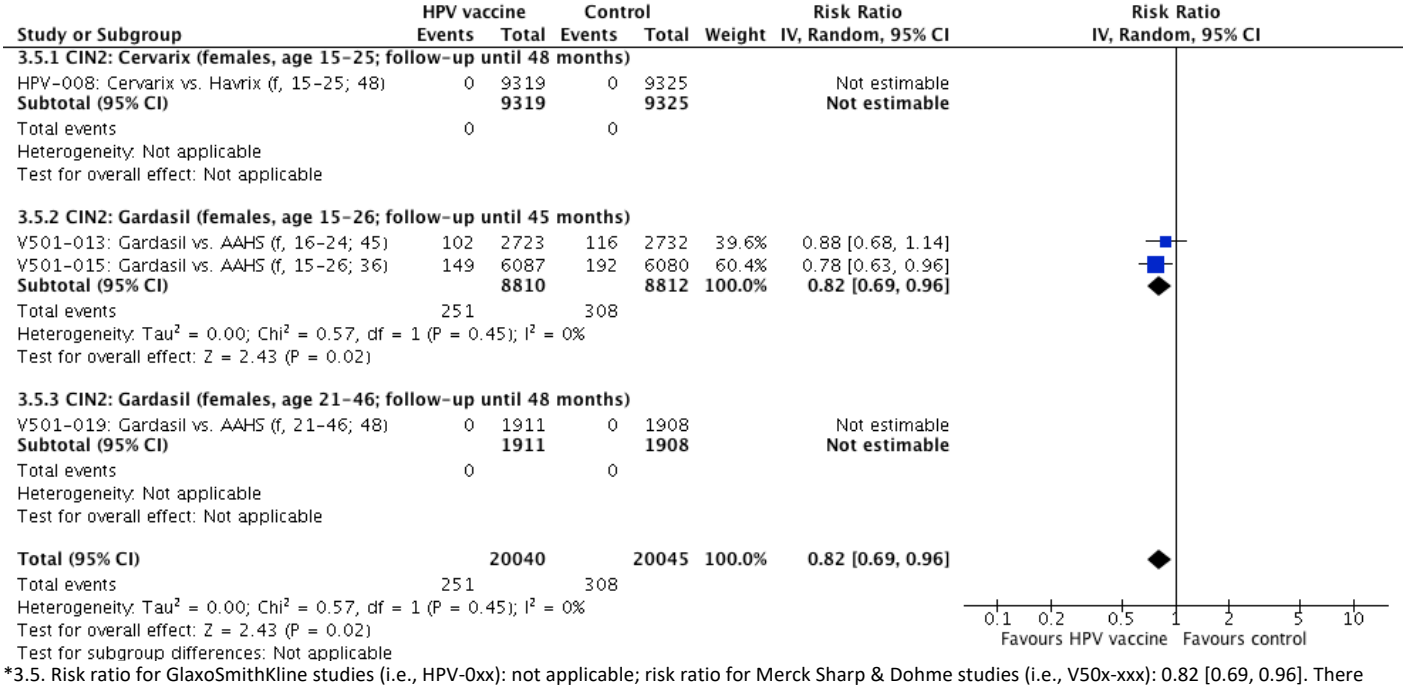
*3.3. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): not applicable; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 3.01 [0.12, 73.85].

3.4. Incidence of HPV-related carcinoma in situ (anal intraepithelial neoplasia grade 3 [AIN3], cervical adenocarcinoma in situ [AIS], cervical intraepithelial neoplasia grade 3 [CIN3], penile intraepithelial neoplasia grade 3 [PIN3], vaginal intraepithelial neoplasia grade 3 [VIN3] and vulvar intraepithelial neoplasia grade 3 [VaIN3]) irrespective of HPV type*: intention to treat analysis



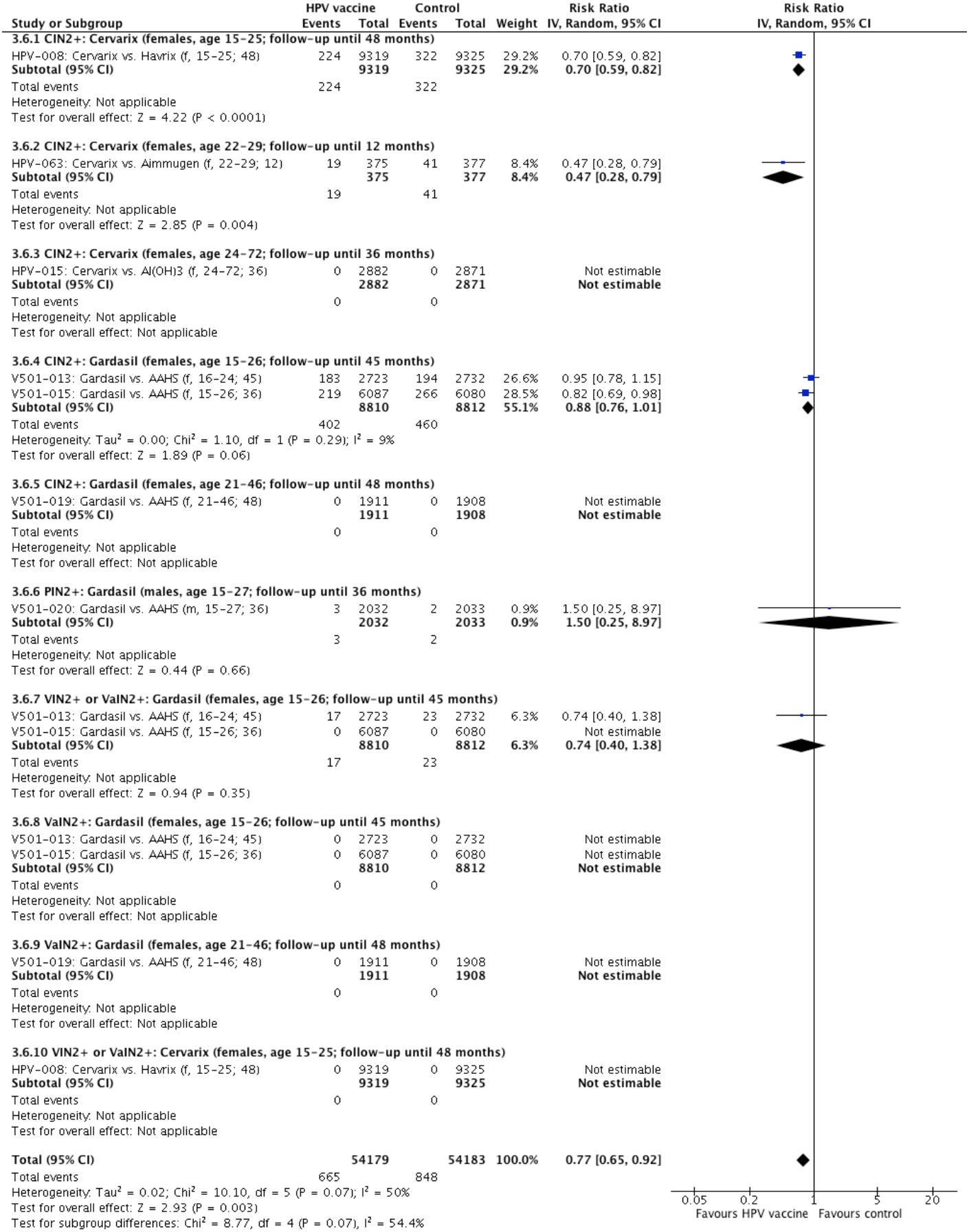
*3.4. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): not applicable; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 0.85 [0.61, 1.19].

3.5. Incidence of HPV-related moderate intraepithelial neoplasia (anal intraepithelial neoplasia grade 2 [AIN2], cervical intraepithelial neoplasia grade 2 [CIN2], penile intraepithelial neoplasia grade 2 [PIN2], vaginal intraepithelial neoplasia grade 2 [VIN2] and vulvar intraepithelial neoplasia grade 2 [VaIN2]) irrespective of HPV type*: intention to treat analysis



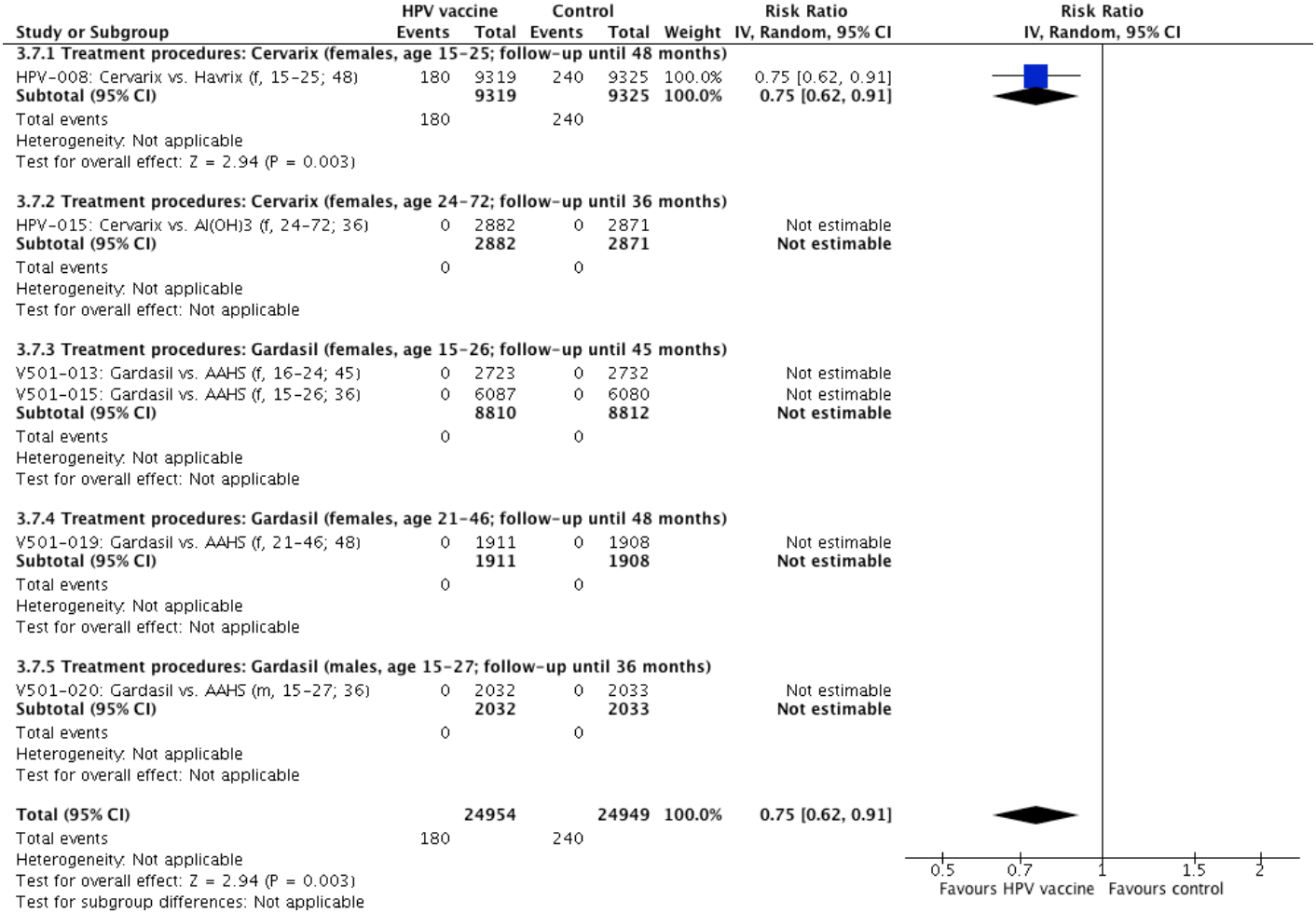
*3.5. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): not applicable; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 0.82 [0.69, 0.96]. There were no reports of AIN2, PIN2, VIN2 or VaIN2 irrespective of HPV type.

3.6. Incidence of HPV-related moderate intraepithelial neoplasia or worse (AIN2$^+$, CIN2$^+$, PIN2$^+$, VIN2$^+$, VaIN2$^+$) irrespective of HPV type*: intention to treat analysis



*3.6. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 0.62 [0.43, 0.89]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 0.87 [0.77, 0.99].

3.7. Number of treatment procedures (both surgical and non-surgical treatment) due to HPV-related diseases irrespective of HPV type*: intention to treat analysis



*3.7. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): **0.75 [0.62, 0.91]**; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): not applicable.

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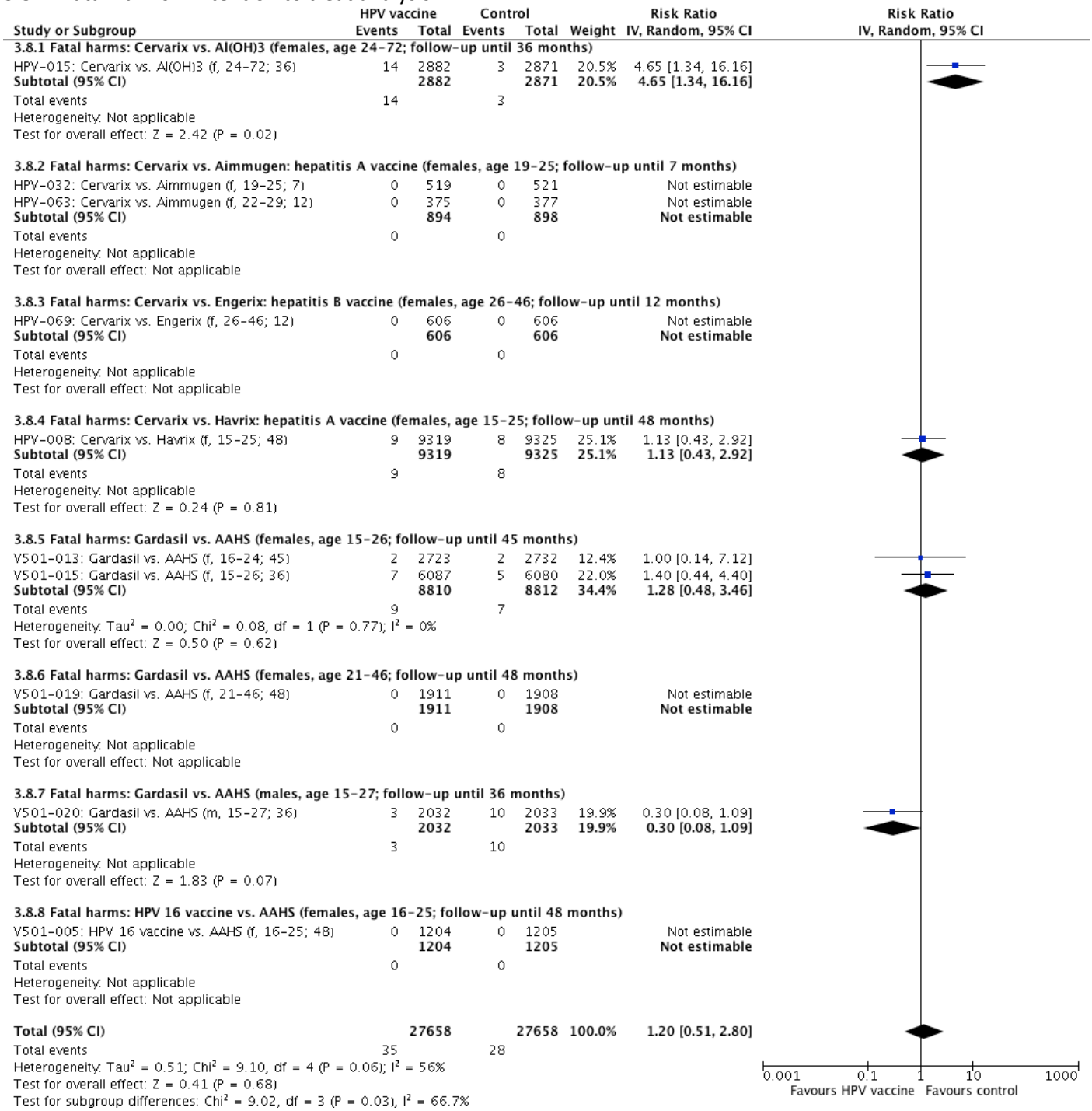
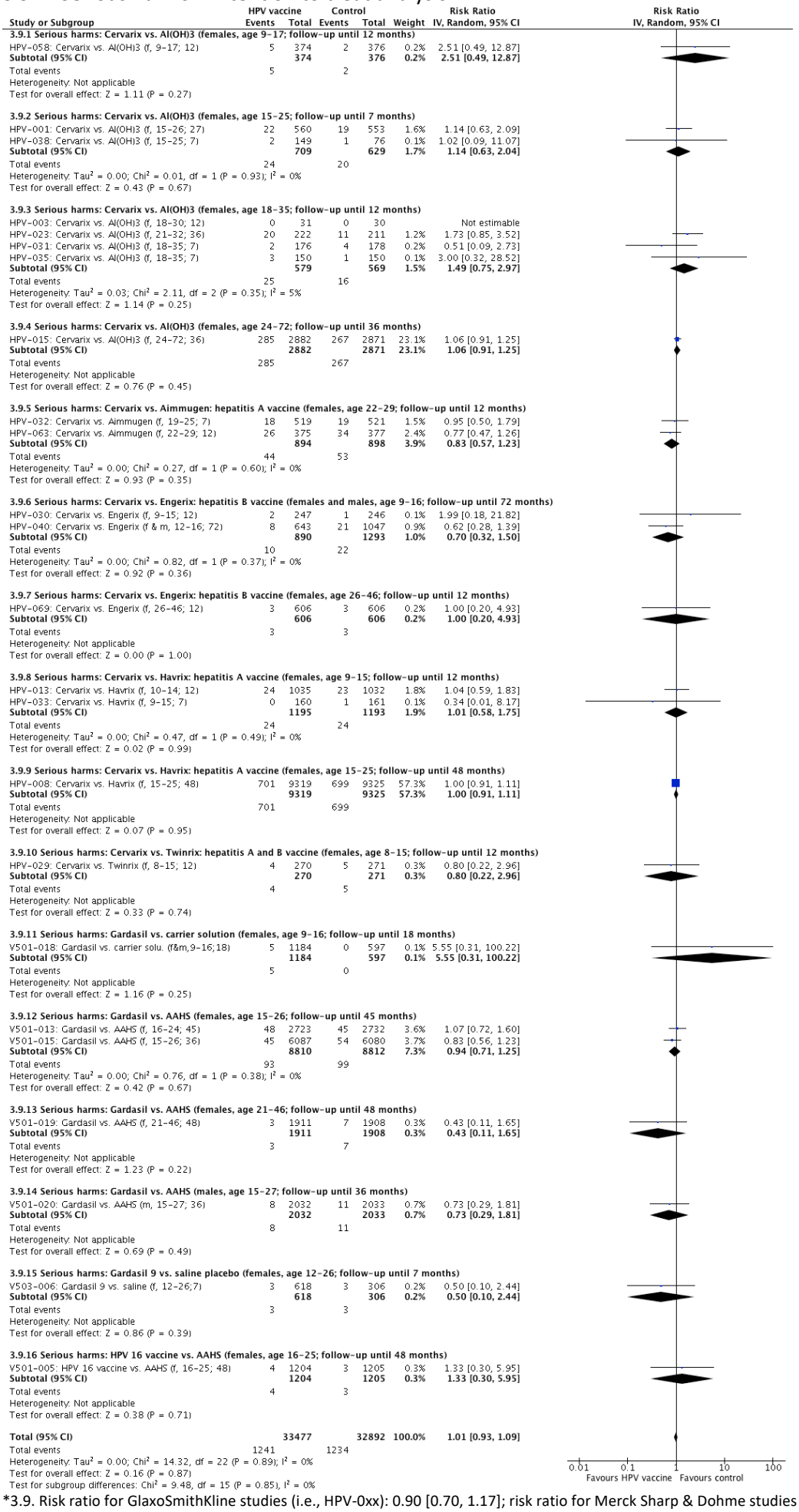
3.8. Fatal harms*: intention to treat analysis



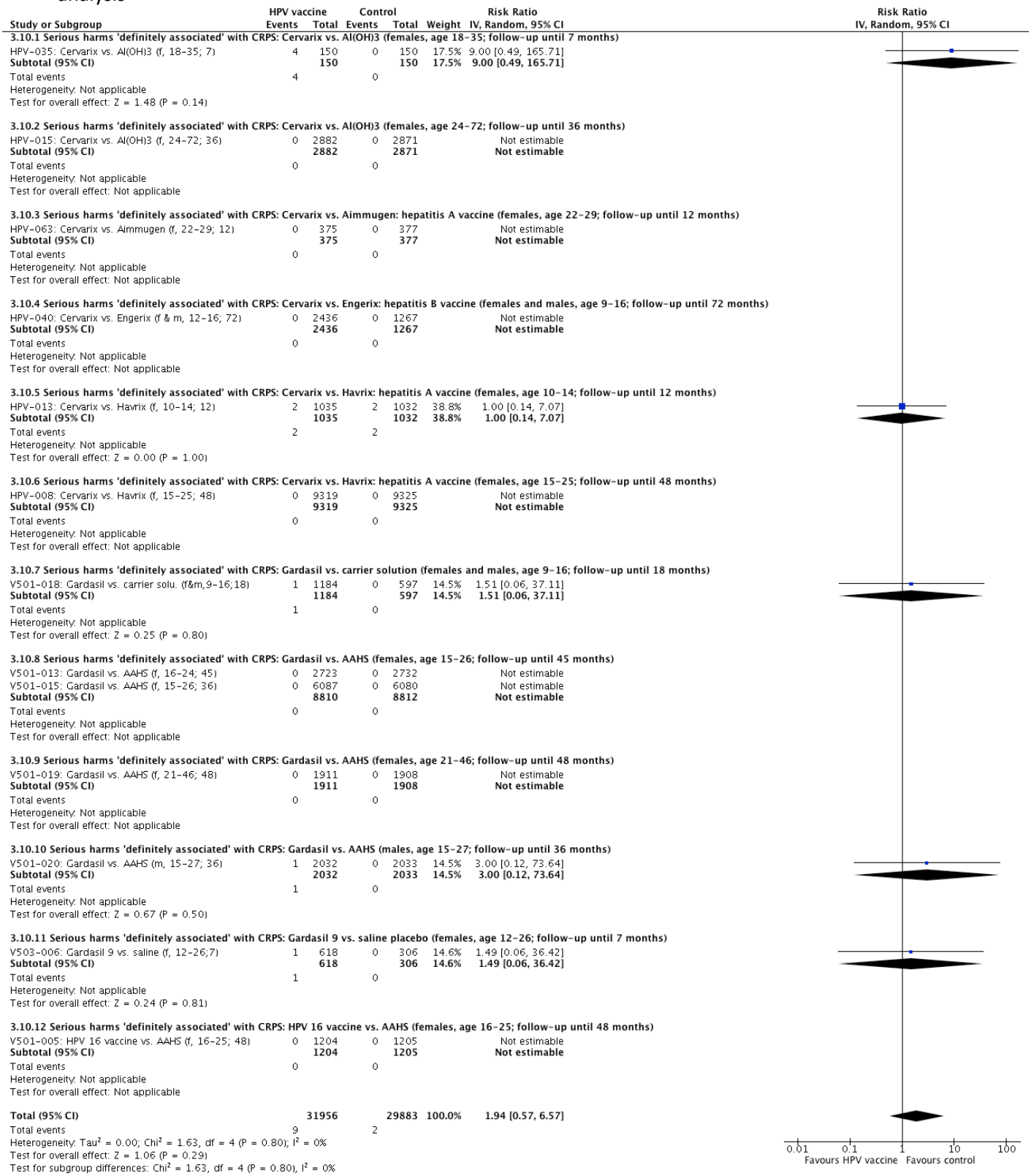
*3.8. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 2.16 [0.54, 8.61]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 0.74 [0.27, 2.05].

3.9. Serious harms*: intention to treat analysis



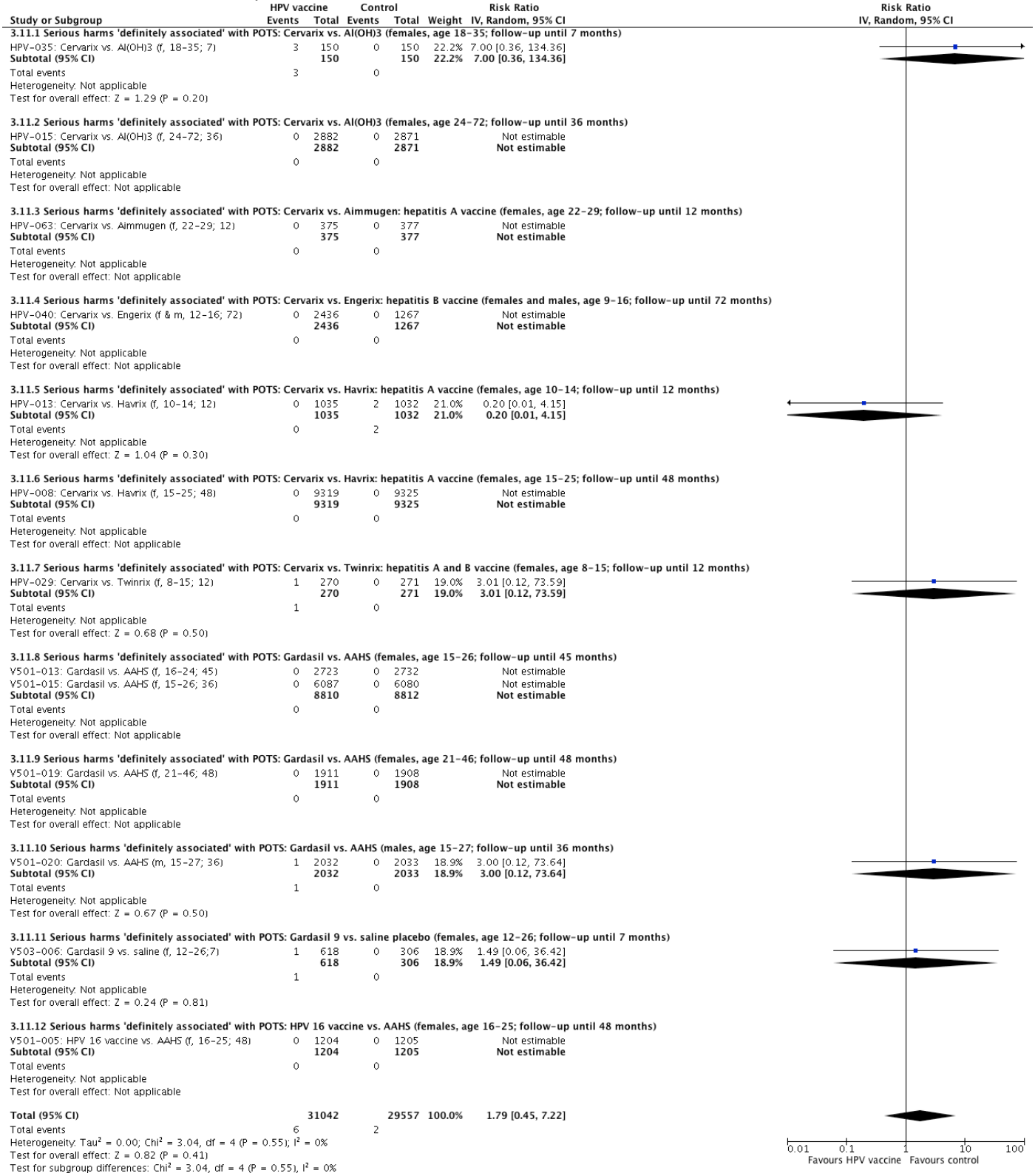
*3.9. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 0.90 [0.70, 1.17]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 1.02 [0.94, 1.10].

3.10. Serious harms judged as 'definitely associated'* with chronic regional pain syndrome (CRPS): intention to treat analysis



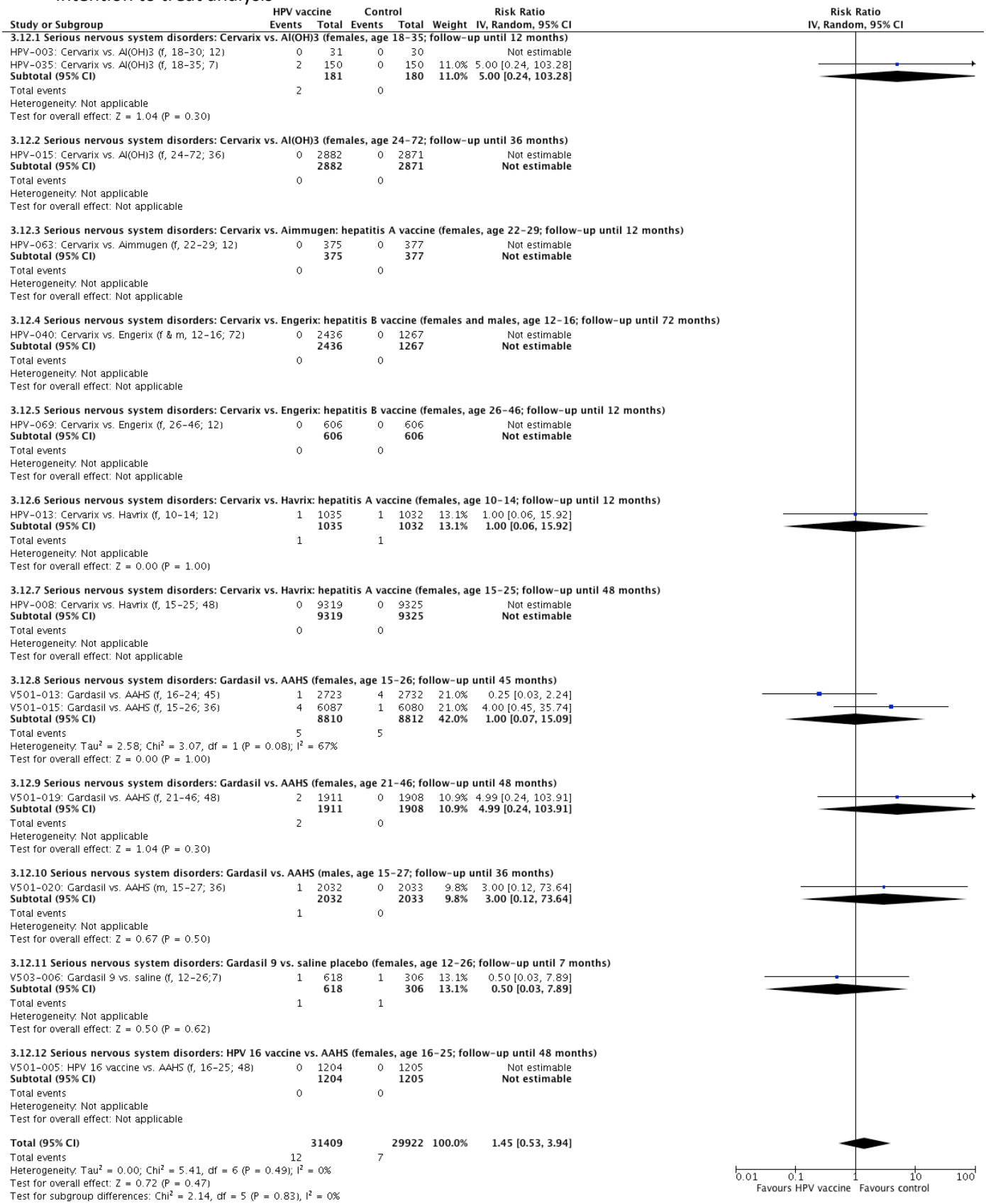
*3.10. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 2.27 [0.28, 18.35]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 1.89 [0.30, 11.99]. We asked a physician with clinical expertise in CRPS to assess the reported MedDRA preferred terms as 'definitely,' 'probably,' 'probably not' or 'definitely not' associated with CRPS. We sent an Excel sheet to the physician with all the reported MedDRA terms. The physician was blinded, as the Excel sheet contained no outcome data. When the physician had assessed all the MedDRA terms, we synthesized the data for those MedDRA terms that the physician judged 'definitely' associated with CRPS and compared it to the reported serious harms.

3.11. Serious harms judged as 'definitely associated'* with postural orthostatic tachycardia syndrome (POTS): intention to treat analysis



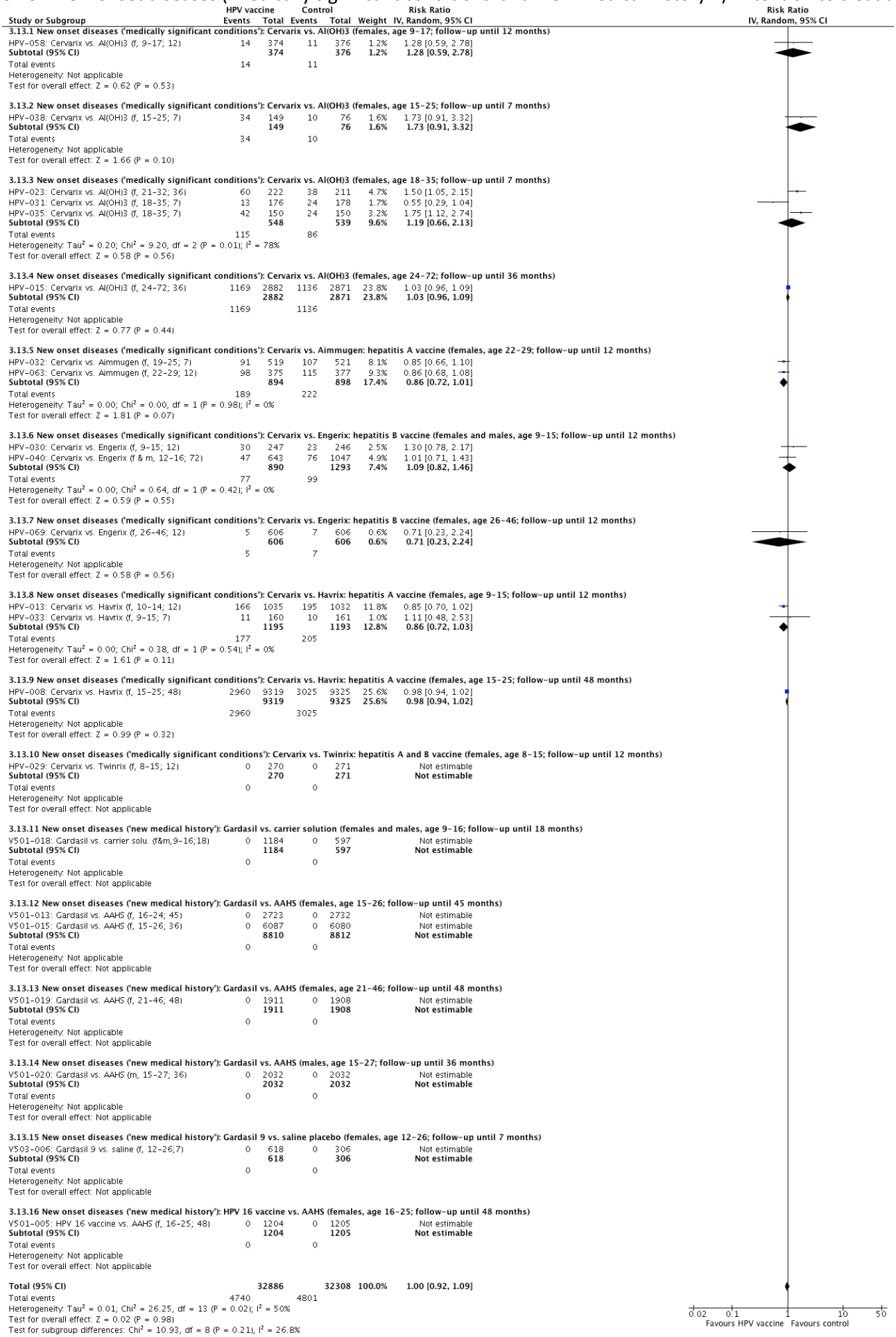
*3.11. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 1.62 [0.19, 13.68]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 2.11 [0.22, 20.29]. We asked a physician with clinical expertise in POTS to assess the reported MedDRA preferred terms as 'definitely,' 'probably,' 'probably not' or 'definitely not' associated with POTS. We sent an Excel sheet to the physician with all the reported MedDRA terms. The physician was blinded, as the Excel sheet contained no outcome data. When the physician had assessed all the MedDRA terms, we synthesized the data for those MedDRA terms that the physician judged 'definitely' associated with POTS and compared it to the reported serious harms.

3.12. Serious harms reported within the MedDRA system organ class 'nervous system disorders (10029205)'*: intention to treat analysis



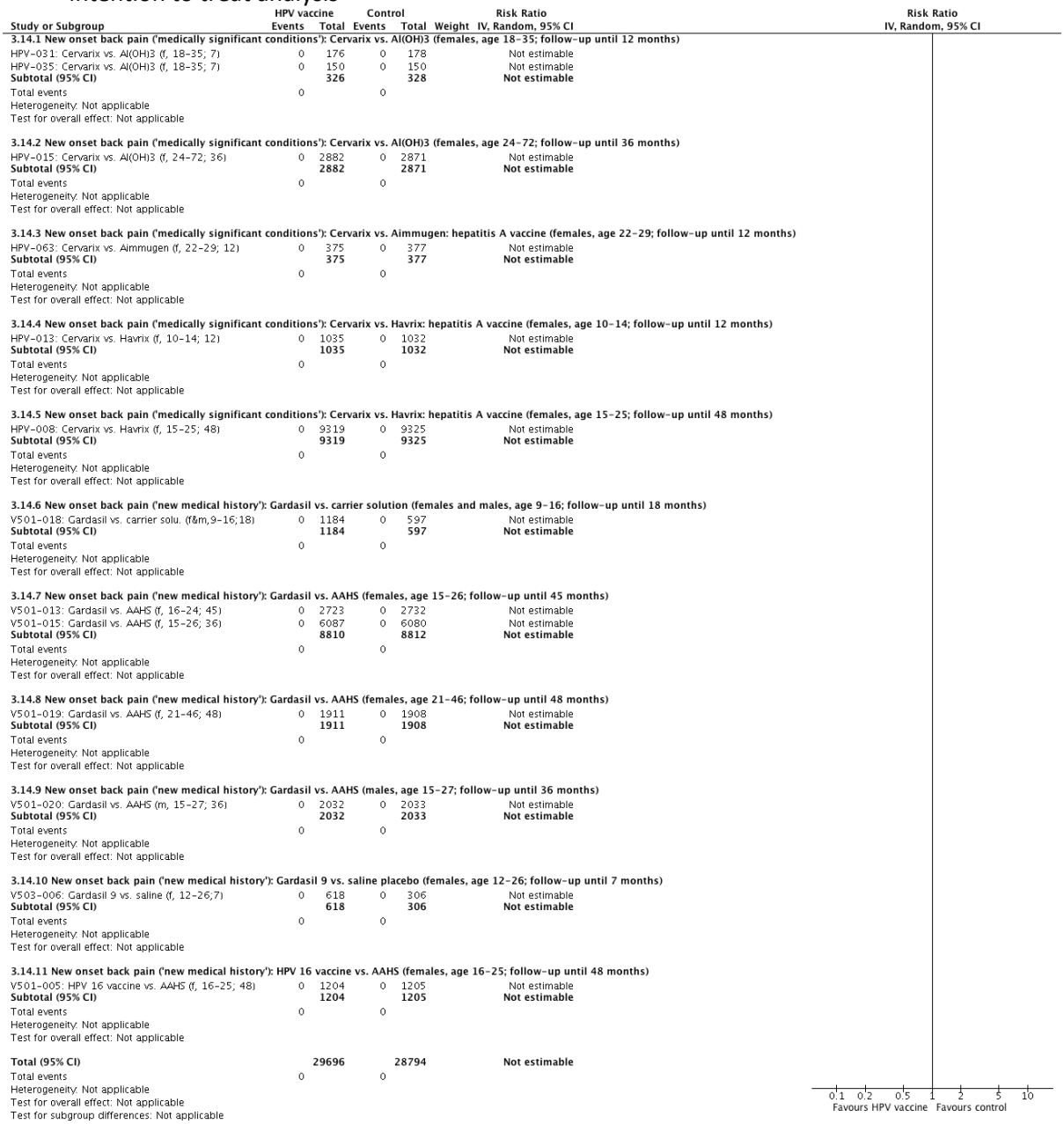
*3.12. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 2.08 [0.27, 16.05]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 1.31 [0.37, 4.60].

3.13. New onset diseases ('medically significant conditions' and 'new medical history'*): intention to treat analysis



*3.13. Risk ratio for 'medically significant conditions' (GlaxoSmithKline): 1.00 [0.92, 1.09]; risk ratio for 'new medical history' (Merck Sharp & Dohme): not applicable.

3.14. New onset diseases most associated with the HPV vaccines (‘medically significant conditions’) - ‘back pain’: intention to treat analysis

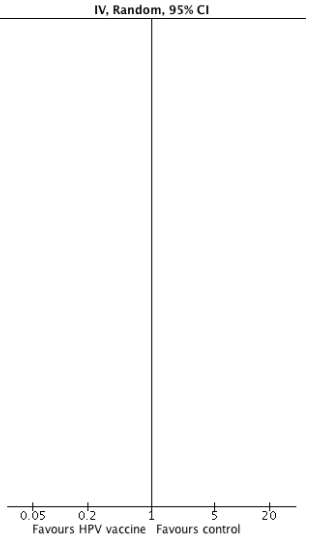


Study or Subgroup	HPV vaccine Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
3.14.1 New onset back pain ('medically significant conditions'): Cervarix vs. Al(OH)3 (females, age 18–35; follow–up until 12 months)						
HPV–031: Cervarix vs. Al(OH)3 (f, 18–35; 7)	0	176	0	178		Not estimable
HPV–035: Cervarix vs. Al(OH)3 (f, 18–35; 7)	0	150	0	150		Not estimable
Subtotal (95% CI)		**326**		**328**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.14.2 New onset back pain ('medically significant conditions'): Cervarix vs. Al(OH)3 (females, age 24–72; follow–up until 36 months)						
HPV–015: Cervarix vs. Al(OH)3 (f, 24–72; 36)	0	2882	0	2871		Not estimable
Subtotal (95% CI)		**2882**		**2871**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.14.3 New onset back pain ('medically significant conditions'): Cervarix vs. Aimmugen: hepatitis A vaccine (females, age 22–29; follow–up until 12 months)						
HPV–063: Cervarix vs. Aimmugen (f, 22–29; 12)	0	375	0	377		Not estimable
Subtotal (95% CI)		**375**		**377**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.14.4 New onset back pain ('medically significant conditions'): Cervarix vs. Havrix: hepatitis A vaccine (females, age 10–14; follow–up until 12 months)						
HPV–013: Cervarix vs. Havrix (f, 10–14; 12)	0	1035	0	1032		Not estimable
Subtotal (95% CI)		**1035**		**1032**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.14.5 New onset back pain ('medically significant conditions'): Cervarix vs. Havrix: hepatitis A vaccine (females, age 15–25; follow–up until 48 months)						
HPV–008: Cervarix vs. Havrix (f, 15–25; 48)	0	9319	0	9325		Not estimable
Subtotal (95% CI)		**9319**		**9325**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.14.6 New onset back pain ('new medical history'): Gardasil vs. carrier solution (females and males, age 9–16; follow–up until 18 months)						
V501–018: Gardasil vs. carrier solu. (f&m,9–16;18)	0	1184	0	597		Not estimable
Subtotal (95% CI)		**1184**		**597**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.14.7 New onset back pain ('new medical history'): Gardasil vs. AAHS (females, age 15–26; follow–up until 45 months)						
V501–013: Gardasil vs. AAHS (f, 16–24; 45)	0	2723	0	2732		Not estimable
V501–015: Gardasil vs. AAHS (f, 15–26; 36)	0	6087	0	6080		Not estimable
Subtotal (95% CI)		**8810**		**8812**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.14.8 New onset back pain ('new medical history'): Gardasil vs. AAHS (females, age 21–46; follow–up until 48 months)						
V501–019: Gardasil vs. AAHS (f, 21–46; 48)	0	1911	0	1908		Not estimable
Subtotal (95% CI)		**1911**		**1908**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.14.9 New onset back pain ('new medical history'): Gardasil vs. AAHS (males, age 15–27; follow–up until 36 months)						
V501–020: Gardasil vs. AAHS (m, 15–27; 36)	0	2032	0	2033		Not estimable
Subtotal (95% CI)		**2032**		**2033**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.14.10 New onset back pain ('new medical history'): Gardasil 9 vs. saline placebo (females, age 12–26; follow–up until 7 months)						
V503–006: Gardasil 9 vs. saline (f, 12–26;7)	0	618	0	306		Not estimable
Subtotal (95% CI)		**618**		**306**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.14.11 New onset back pain ('new medical history'): HPV 16 vaccine vs. AAHS (females, age 16–25; follow–up until 48 months)						
V501–005: HPV 16 vaccine vs. AAHS (f, 16–25; 48)	0	1204	0	1205		Not estimable
Subtotal (95% CI)		**1204**		**1205**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**29696**		**28794**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						

*3.14. Risk ratio for 'medically significant conditions’ (GlaxoSmithKline): not applicable; risk ratio for ‘new medical history’ (Merck Sharp & Dohme): not applicable.

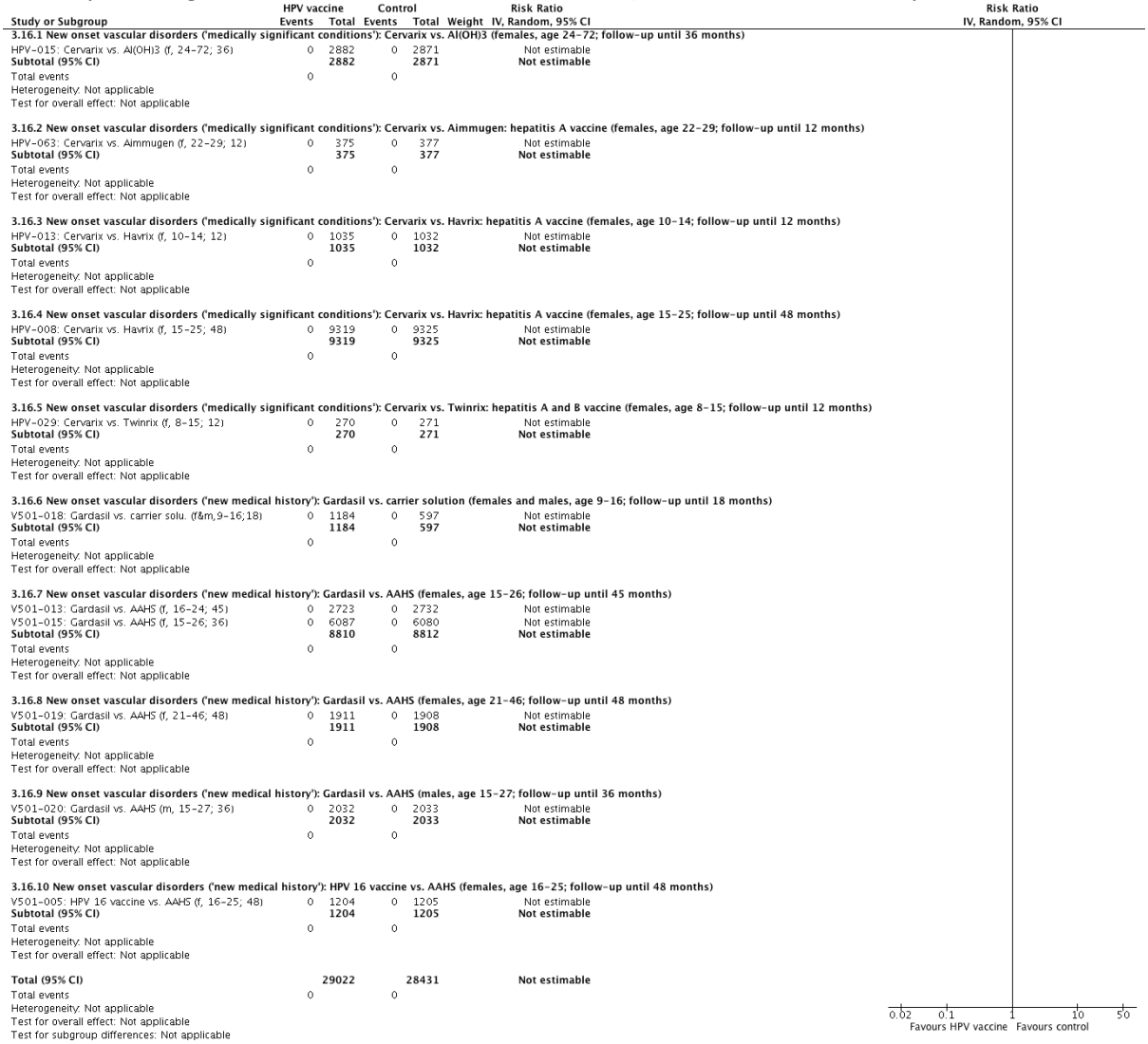
3.15. New onset diseases most inversely associated with the HPV vaccines ('new medical history') - 'vaginal infection': intention to treat analysis

Study or Subgroup	HPV vaccine Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
3.15.1 New onset vaginal infection ('new medical history'): Gardasil vs. carrier solution (females and males, age 9-16; follow-up until 18 months)						
V501-018: Gardasil vs. carrier solu. (f&m,9-16;18)	0	1184	0	597		Not estimable
Subtotal (95% CI)		**1184**		**597**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.15.2 New onset vaginal infection ('new medical history'): Gardasil vs. AAHS (females, age 15-26; follow-up until 45 months)						
V501-013: Gardasil vs. AAHS (f, 16-24; 45)	0	2723	0	2732		Not estimable
V501-015: Gardasil vs. AAHS (f, 15-26; 36)	0	6087	0	6080		Not estimable
Subtotal (95% CI)		**8810**		**8812**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.15.3 New onset vaginal infection ('new medical history'): Gardasil vs. AAHS (females, age 21-46; follow-up until 48 months)						
V501-019: Gardasil vs. AAHS (f, 21-46; 48)	0	1911	0	1908		Not estimable
Subtotal (95% CI)		**1911**		**1908**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.15.4 New onset vaginal infection ('new medical history'): Gardasil 9 vs. saline placebo (females, age 12-26; follow-up until 7 months)						
V503-006: Gardasil 9 vs. saline (f, 12-26;7)	0	618	0	306		Not estimable
Subtotal (95% CI)		**618**		**306**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**12523**		**11623**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



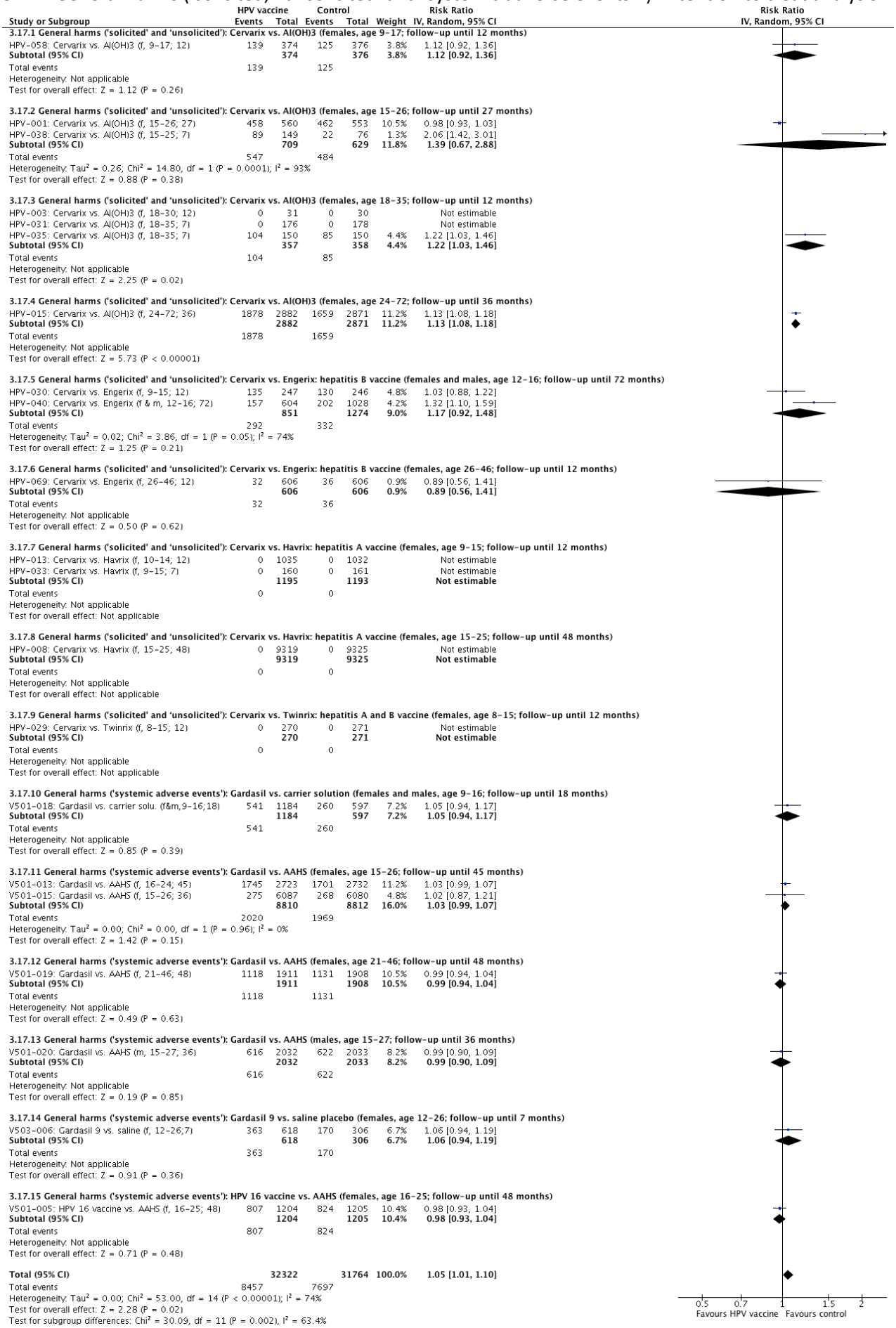
*3.15. Risk ratio for 'medically significant conditions' (GlaxoSmithKline): not applicable; risk ratio for 'new medical history' (Merck Sharp & Dohme): not applicable.

3.16. New onset diseases ('medically significant conditions' and 'new medical history') reported within the MedDRA system organ class ‘vascular disorders (10047065)': intention to treat analysis



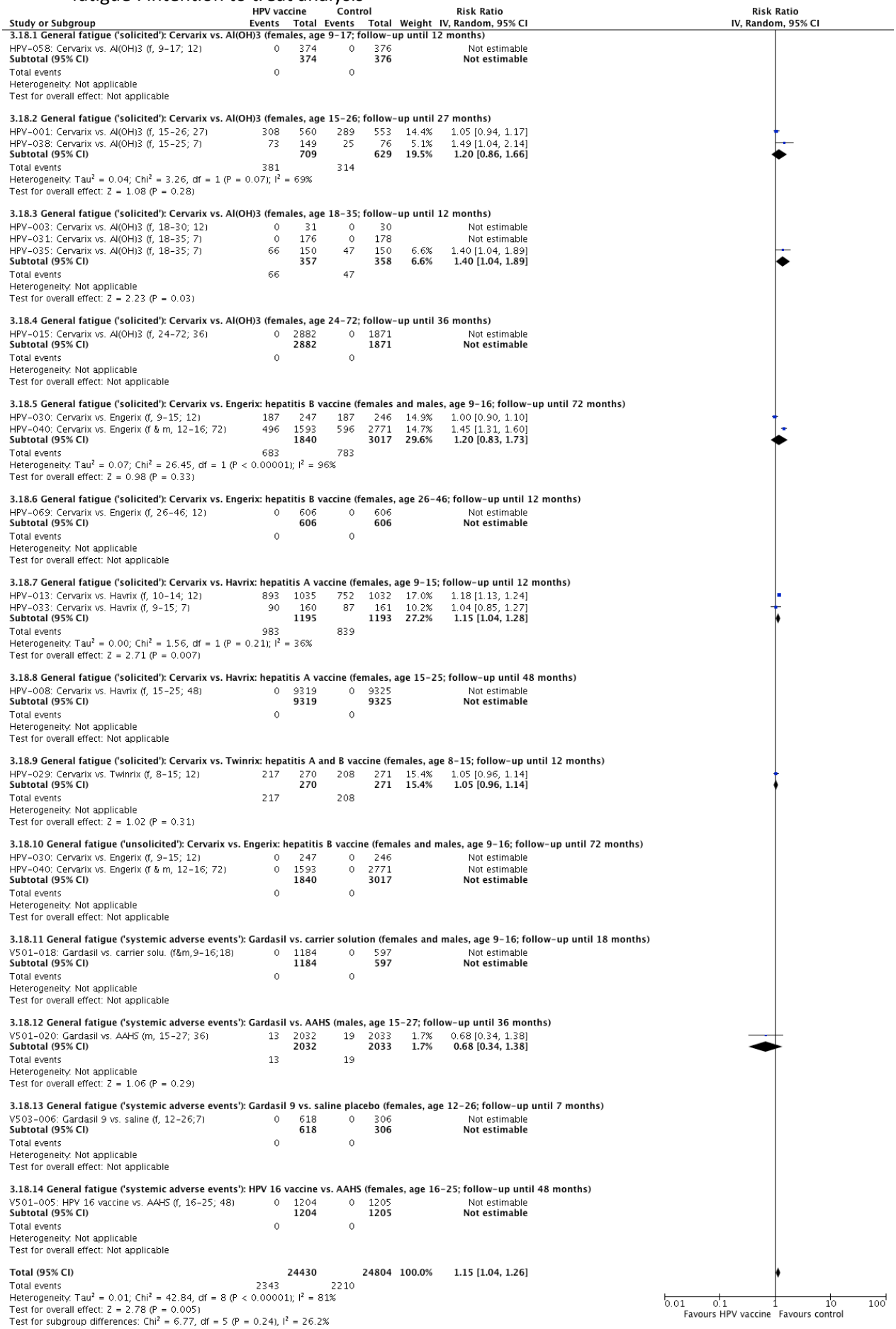
*3.16. Risk ratio for 'medically significant conditions’ (GlaxoSmithKline): not applicable; risk ratio for ‘new medical history’ (Merck Sharp & Dohme): not applicable.

3.17. General harms ('solicited,' 'unsolicited' and 'systemic adverse events'*): intention to treat analysis



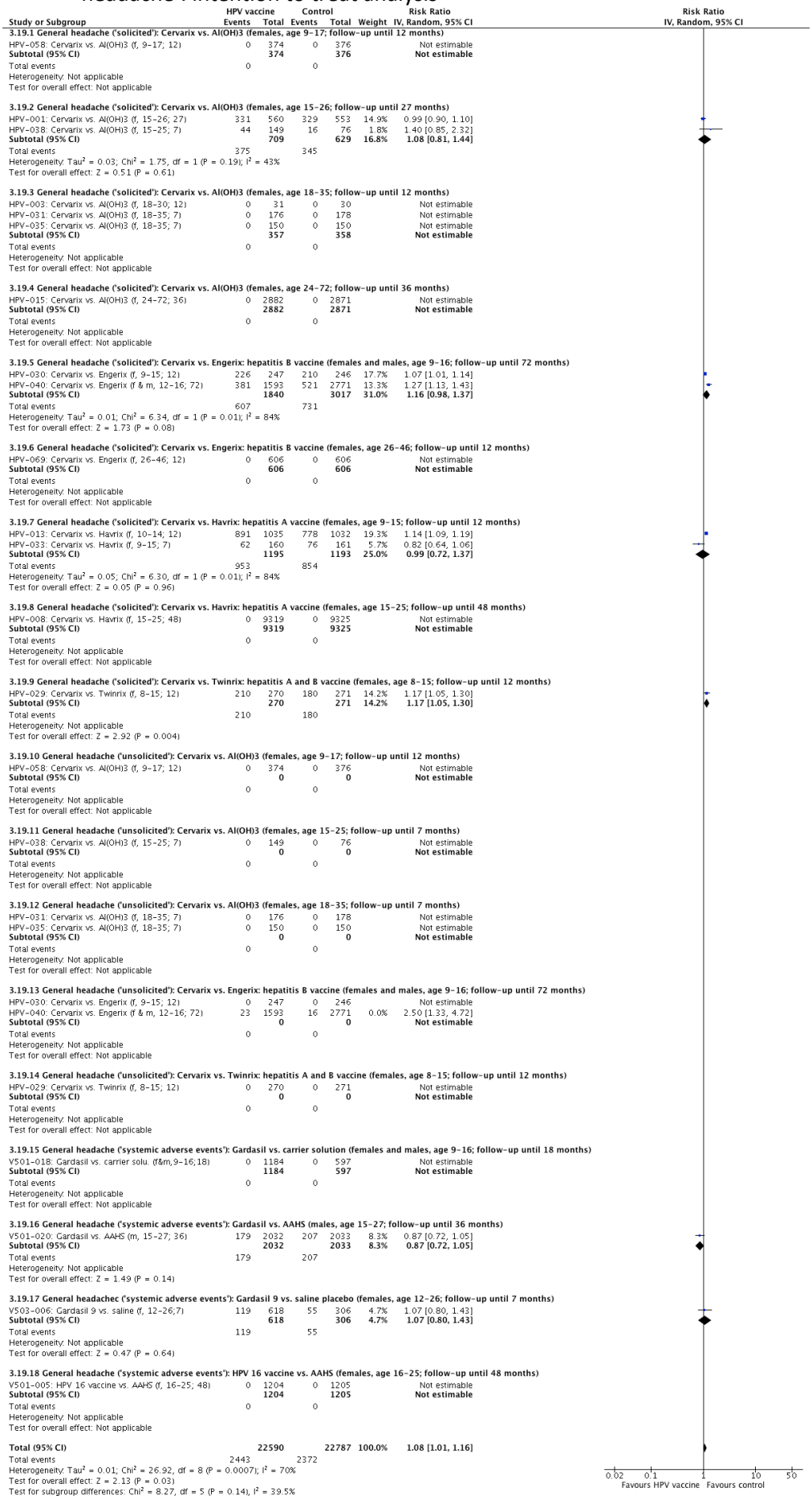
*3.17. Risk ratio for 'solicited' (GlaxoSmithKline): **1.14 [1.03, 1.26]**; risk ratio for 'unsolicited' (GlaxoSmithKline): 1.01 [0.98, 1.03]; risk ratio for 'systemic adverse events' (Merck Sharp & Dohme): 1.01 [0.97, 1.04]. To avoid double counting of participants in the total risk ratio estimate, we only included 'solicited' adverse events if the journal publication also had reported 'unsolicited' adverse events.

3.18. General harms most associated with the HPV vaccines ('solicited,' 'unsolicited' and 'systemic adverse events'*) - 'fatigue': intention to treat analysis



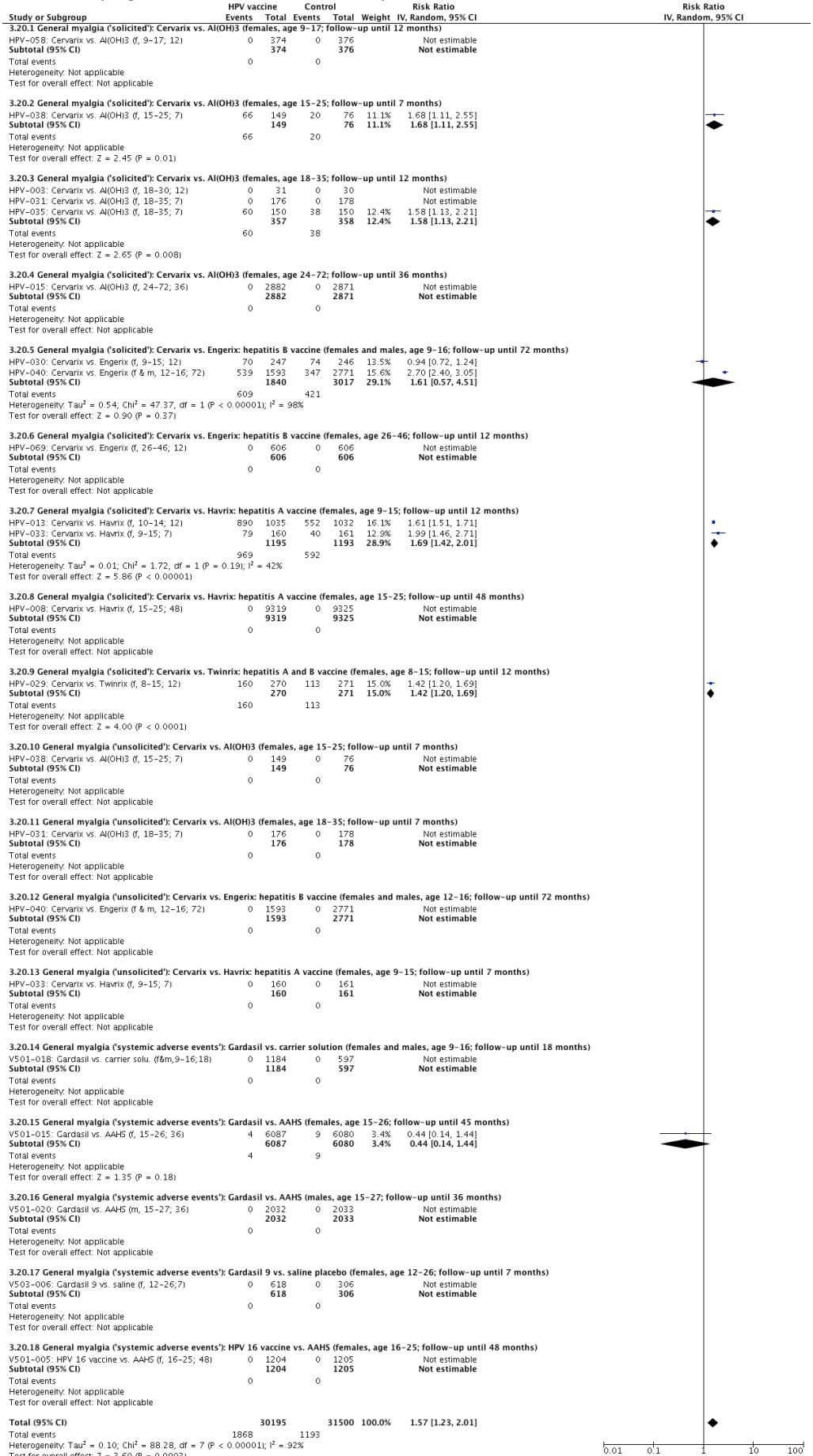
*3.18. Risk ratio for 'solicited' (GlaxoSmithKline): **1.16 [1.05, 1.28]**; risk ratio for 'unsolicited' (GlaxoSmithKline): not applicable; risk ratio for 'systemic adverse events' (Merck Sharp & Dohme): 0.68 [0.34, 1.38]. To avoid double counting of participants in the total risk ratio estimate, we excluded the 'unsolicited' adverse events from total risk ratio estimate for studies that reported 'solicited' adverse events.

3.19. General harms most associated with the HPV vaccines ('solicited,' 'unsolicited' and 'systemic adverse events'*) - 'headache': intention to treat analysis



*3.19. Risk ratio for 'solicited' (GlaxoSmithKline): **1.11 [1.03, 1.19]**; risk ratio for 'unsolicited' (GlaxoSmithKline): **2.50 [1.33, 4.72]**; risk ratio for 'systemic adverse events' (Merck Sharp & Dohme): 0.94 [0.76, 1.14]. To avoid double counting of participants in the total risk ratio estimate, we excluded the 'unsolicited' adverse events from total risk ratio estimate for studies that reported 'solicited' adverse events.

3.20. General harms most associated with the HPV vaccines ('solicited,' 'unsolicited' and 'systemic adverse events'*) - 'myalgia': intention to treat analysis



*3.20. Risk ratio for 'solicited' (GlaxoSmithKline): **1.64 [1.29, 2.10]**; risk ratio for 'unsolicited' (GlaxoSmithKline): not applicable; risk ratio for 'systemic adverse events' (Merck Sharp & Dohme): 0.44 [0.14, 1.44]. To avoid double counting of participants in the total risk ratio estimate, we excluded the 'unsolicited' adverse events from total risk ratio estimate for studies that reported 'solicited' adverse events.