

SEARCHES

Records identified from database search:



Date: November 19, 2014

Keyword: nalmefene
Filters activated: Clinical Trial

Results: 65 references



Date: November 21, 2014

KEY (nalmefen* OR 6-desoxy-6-methylenaltrexone) AND (LIMIT-TO (EXACTKEYWORD , "Human") OR LIMIT-TO (EXACTKEYWORD , "Humans")) AND (LIMIT-TO (EXACTKEYWORD , "Clinical trial") OR LIMIT-TO (EXACTKEYWORD , "Controlled clinical trial") OR LIMIT-TO (EXACTKEYWORD , "Randomized controlled trial") OR LIMIT-TO (EXACTKEYWORD , "Major clinical study") OR LIMIT-TO (EXACTKEYWORD , "Clinical Trials") OR LIMIT-TO (EXACTKEYWORD , "Clinical article")) AND (EXCLUDE (EXACTKEYWORD , "Nonhuman") OR EXCLUDE (EXACTKEYWORD , "Animals")) AND (EXCLUDE (EXACTKEYWORD , "Review"))

Results: 129 references



Date: November 19, 2014

Keyword: nalmefene
Filters activated: Trials

Results: 89 references

Date: November 27, 2014

Keyword: nalmefene

Results: 11 references
Retained: 3/8 references
NCT01969617 (COMPLETED) → EXCLUDED
NCT00811720 (ESENSE1)
NCT00812461 (ESENSE2)
NCT00811941 (SENSE)
NCT02197598 (RECRUITING) → EXCLUDED
NCT00000437 (COMPLETED) → EXCLUDED
NCT00000450 (COMPLETED) → EXCLUDED
NCT02195817 (RECRUITING) → EXCLUDED



Date: November 27, 2014

Keyword: nalmefene

Results: 1 reference
Retained: 0 reference

Lundbeck Clinical Trial Registry

Date: November 27, 2014

Keyword: nalmefene

Results: 3 references
Retained: 3 references
Study ID: 12023A (ESENSE2)
Study ID: 12014A (ESENSE1)
Study ID: 12013A (SENSE)

Date: December 2, 2014

Sent here:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/landing/ask_ema_landing_page.jsp&mid=WC0b01ac05806499f0

Request Reference Number: ASK-6656

Query:

Dear Sirs,

We are currently working on a meta-analysis to assess the efficacy of Nalmefene in the treatment of adults alcohol dependence in order to reduce alcohol consumption (Protocol Registration number on PROSPERO: CRD42014014853, http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014014853).

We carried out a literature search aimed at identifying the RCTs eligible for our analysis. This search was conducted in PubMed, Embase and the Cochrane Library. We also searched the ClinicalTrials.gov database and other relevant websites. Presently, we are attempting to identify further RCTs.

Would you be able to tell us if any clinical trial evaluating Nalmefene in the treatment of adults alcohol dependence was declared to your agency? If so, we would be very grateful if you could send us a copy of the results that are available. They will be carefully referenced.

We look forward to your answering and we thank you in advance.

We would like to express our gratitude for all your help in this matter,

Dr Florian Naudet, MD, PhD

Centre d'Investigation Clinique CIC-P INSERM 1414, Hôpital de Pontchaillou, Centre Hospitalier Universitaire de Rennes & Université de Rennes 1
2 Rue Henri le Guilloux 35000 Rennes
Rennes, France
Florian.NAUDET@chu-rennes.fr

Results: 8 references

Retained: 7 references



Date: December 2, 2014

Sent here:

Food and Drug Administration (FDA)
Sarah Kotler, Acting Director
Division of Freedom of Information, OES
U.S. Food & Drug Administration
5630 Fishers Lane
Room-1035
Rockville, Maryland 20857
301-796-3900 (main)
301-827-9267 (fax)

Query:

Food and Drug Administration (FDA)
Sarah Kotler, Acting Director
Division of Freedom of Information, OES
U.S. Food & Drug Administration
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Room-1035
Rockville, Maryland 20857
301-796-3900 (main)
301-827-9267 (fax)

Rennes, December 2014 the 2nd,

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We carried out a literature search aimed at identifying the RCTs eligible for our analysis. This search was conducted in PubMed, Embase and the Cochrane Library. We also searched the ClinicalTrials.gov database and other relevant websites. Presently, we are attempting to identify further RCTs.

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Dr Florian Naudet, MD, PhD

Service de psychiatrie adulte et de psychologie médicale

Centre d'Investigation Clinique CIC-P INSERM 1414, Hôpital de Pontchaillou, Centre Hospitalier Universitaire de
Rennes & Université de Rennes 1

2 Rue Henri le Guilloux 35000 Rennes

Rennes, France

Florian.NAUDET@chu-rennes.fr

Results: 0 reference

Answer from FDA:

“My apologies. I had to be unexpectedly away from the office. Let me try and explain some of the issues with your FOIA request 2015-71. You are seeking information about whether there are any trials currently in process about a particular indication. FDA does not discuss information or release information about pending trials or applications. This type of information is generally considered to be confidential commercial information and therefore not releasable before a product is approved. I searched to see if we had any approved drug products for the treatment you have specified and I don't see any for this product under the product name Nalfemene. There is a product Vivitrol (naltrexone) which was approved for a similar indication. If you would like the review package for that product we would be happy to send that to you under FOIA. Please confirm whether you would like the Vivitrol approval package.”

SUMMARY OF INCLUDED STUDIES

WebApp 1. Summary of included studies evaluating the efficacy of nalmefene in the treatment of adult alcohol dependence (main and sensitivity analyses).

Study (EMA Study ID)	Participants	Nalmefene Dose*	Study Duration (Weeks)	Sponsor	Health Outcomes Reported in the Publication	Number of Patients	Age (Years), Mean ± Standard Deviation	Sex (Women), <i>n</i> (Percent)
Gual et al. [24] (12023A)†	“Patients were recruited from in- and out-patient clinics, from the study site’s patient pool, and by spontaneous referrals to the study site.”	20 mg/d (as needed)	24	Lundbeck	No	Nalmefene: 358; placebo: 360	Nalmefene: 45.1 ± 10.7; placebo: 44.4 ± 10.7	Nalmefene: 92 (26%); placebo: 104 (29%)
Mann et al. [25] (12014A)†	“Patients were recruited from in- and out-patient clinics, including both spontaneous referrals and referrals resulting from special advertisements.”	20 mg/d (as needed)	24	Lundbeck	No	Nalmefene: 306; placebo: 298	Nalmefene: 51.0 ± 10.1; placebo: 52.1 ± 9.0	Nalmefene: 102 (33%); placebo: 96 (32%)
Karhuvaara et al. [26] (CPH-101-801)†	“The subjects were recruited mainly by means of advertisements posted in newspapers.”	10 to 40 mg/d (as needed)	28	Biotie Therapies	No	Nalmefene: 242; placebo: 161	Nalmefene: 49.5 ± 9.1; placebo: 48.8 ± 8.4	Nalmefene: 46 (19%); placebo: 29 (18%)
CPH-101-0701†	“Subjects were recruited through 3 channels: subjects were already patients of the investigator/referred to the sites by general practitioners/contacted the sites after seeing an advertisement.”	10 to 40 mg/d (as needed)	28	Biotie Therapies	Unpublished	Nalmefene: 85; placebo: 82	Nalmefene: 45.8 ± 8.6; placebo: 44.8 ± 10.4	Nalmefene: 33 (39%); placebo: 31 (38%)
van den Brink et al. [27] (12013A)†	“Patients were recruited from outpatient clinics, from the study sites’ own patient pool, by referrals to the study site, or by using advertisements.”	20 mg/d (as needed)	52 + 4 wk of safety follow-up	Lundbeck	No	Nalmefene: 509; placebo: 166	Nalmefene: 44.3 ± 11.2; placebo: 44.3 ± 12	Nalmefene: 116 (23%); placebo: 39 (23%)
Mason et al. [28]‡	“Potential subjects responding to Public Service Announcements advertising studies for alcoholics were evaluated for study inclusion and exclusion criteria.”	20 mg twice daily	12	Baker Norton Pharmaceuticals	No	Nalmefene: 7; placebo: 7	42.0 ± 9.4**	6 (29%)**
Mason et al. [29]‡	“Subjects were alcohol-dependent outpatients recruited primarily through advertisements and press releases.”	10 mg or 40 mg twice daily	12	National grant and Ivax Corporation	No	Nalmefene: 70; placebo: 35	Nalmefene: 41.9 ± 8.2; placebo: 41.7 ± 9.9	Nalmefene: 22 (31%); placebo: 13 (37%)
Anton et al. [30] (CPH-101-0299)‡	“Individuals were recruited from clinical referrals and direct advertisement.”	20 mg/d	12	Biotie Therapies	No	Nalmefene: 66; placebo: 68	Nalmefene: 46.5 ± 10.9; placebo: 45.1 ± 11.1	Nalmefene: 18 (27%); placebo: 15 (22%)
CPH-101-0399‡	“Male and female subjects responding to advertisements were evaluated for their eligibility to participate.”	40 mg/d	16	Contral Pharma	Unpublished	Nalmefene: 50; placebo: 50	Nalmefene: 50.0 ± 9.0; placebo: 48.0 ± 9.0	Nalmefene: 6 (12%); placebo: 11 (22%)

*Expressed in nalmefene HCL. Nalmefene HCL 20 mg corresponds to 18.06 mg nalmefene base. **Only overall data available.

†Studies included in the main and sensitivity analyses. ‡Studies included only in sensitivity analysis.

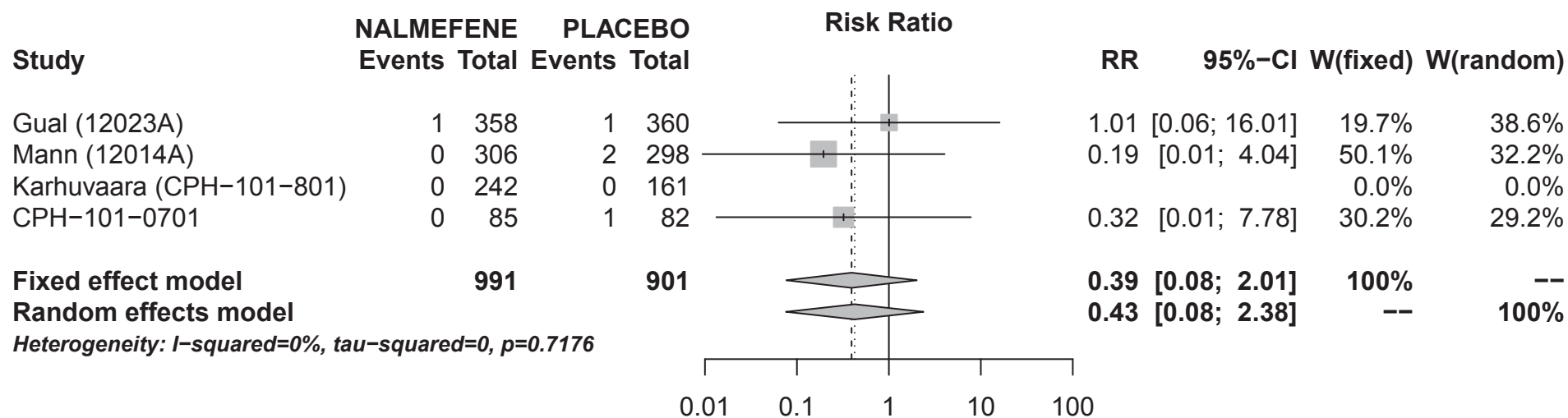
WebApp 2. Quality assessment of included studies evaluating the efficacy of nalmefene in the treatment of adult alcohol dependence.

Study	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other source of bias
Gual et al. (12023A)	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Mann et al. (12014A)	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Karhuvaara et al. (CPH-101-801)	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
CPH-101-0701	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
van den Brink et al. (12013A)	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Mason et al. (1994)	Unclear risk	Unclear risk	Low risk	Unclear risk	High risk	Low risk
Mason et al. (1999)	Unclear risk	Unclear risk	Low risk	Unclear risk	High risk	Low risk
Anton et al. (CPH-101-0299)	Unclear risk	Low risk	Low risk	High risk	Low risk	Low risk
CPH-101-0399	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

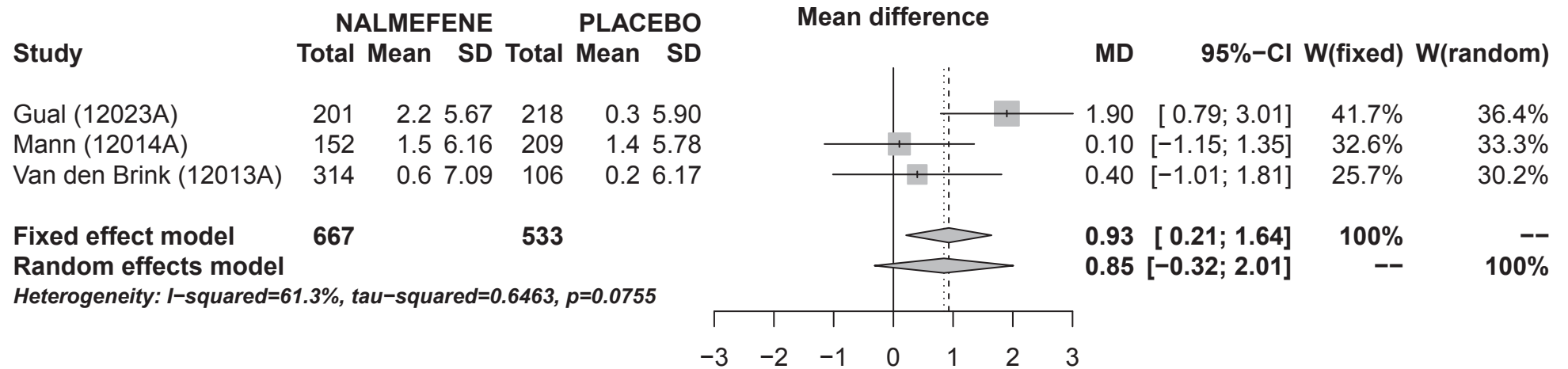
Each study was assessed for methodological quality using the Cochrane Collaboration tool for assessing risk of bias.

MAIN ANALYSIS

Mortality at 6 months

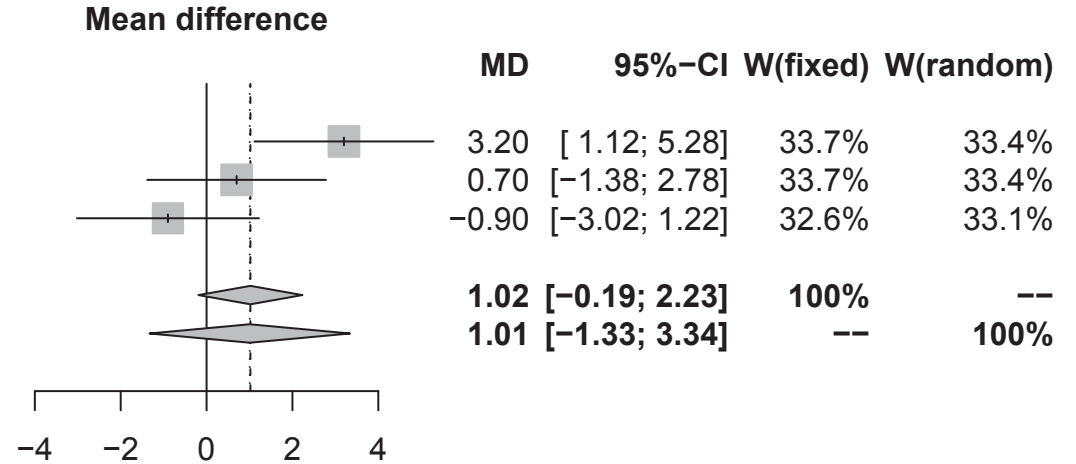


QoL:SF-36 Physical component summary score at 6 months

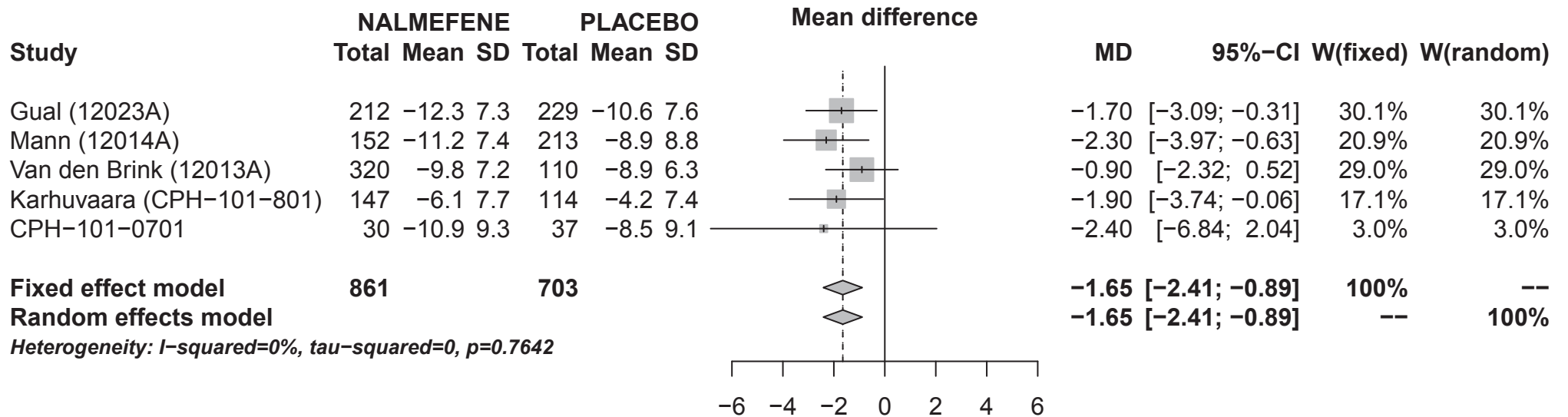


QoL:SF-36 Mental component summary score at 6 months

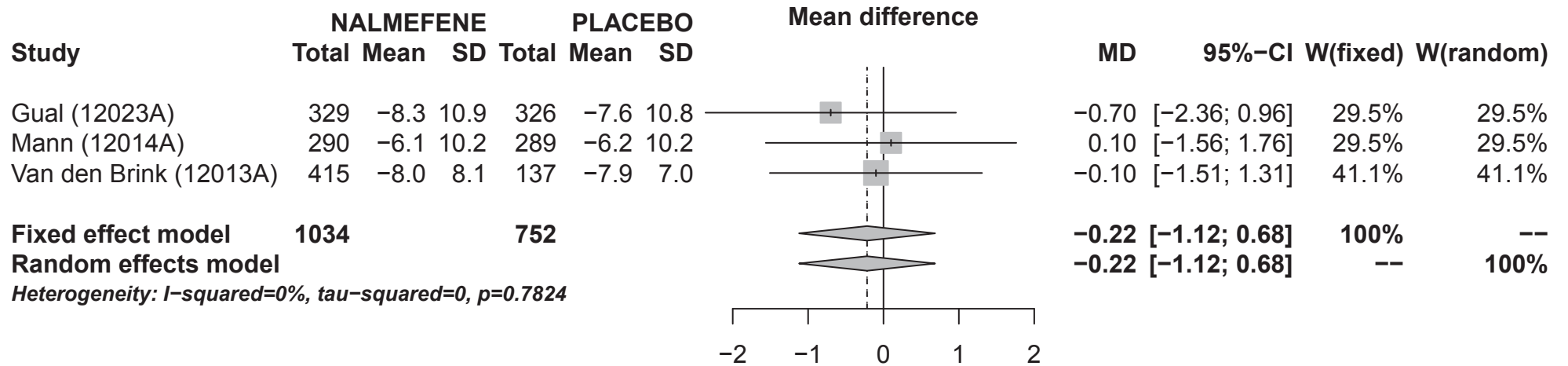
Study	NALMEFENE			PLACEBO			Mean difference	MD	95%-CI	W(fixed)	W(random)
	Total	Mean	SD	Total	Mean	SD					
Gual (12023A)	201	6.8	11.34	218	3.6	10.34					
Mann (12014A)	152	3.2	9.86	209	2.5	10.12					
Van den Brink (12013A)	314	4.2	10.63	106	5.1	9.26					
Fixed effect model	667			533							
Random effects model											
<i>Heterogeneity: I-squared=73.2%, tau-squared=3.114, p=0.0241</i>											



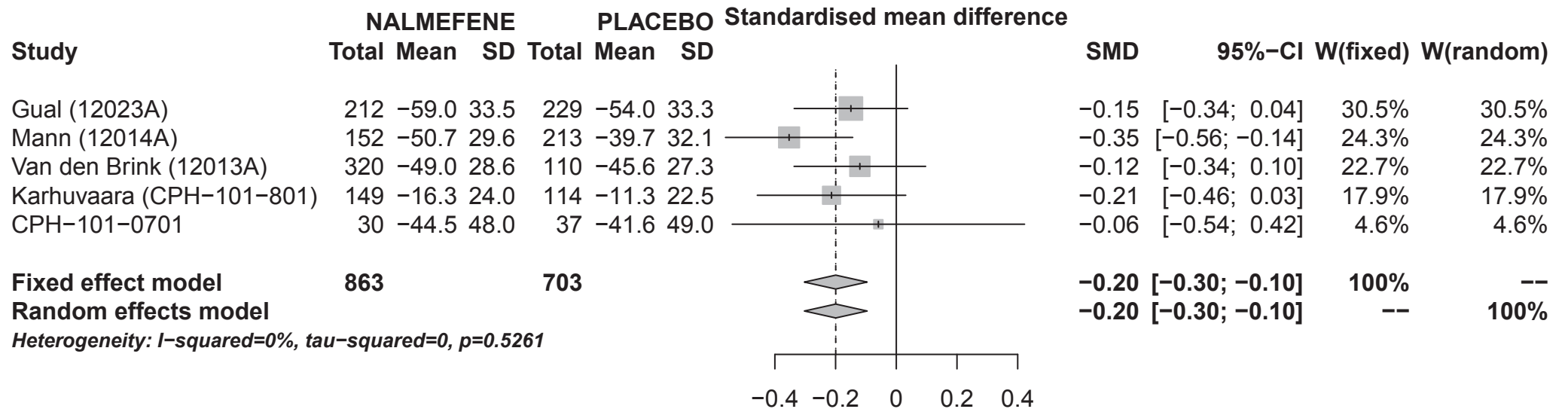
Monthly number of HDDs at 6 months



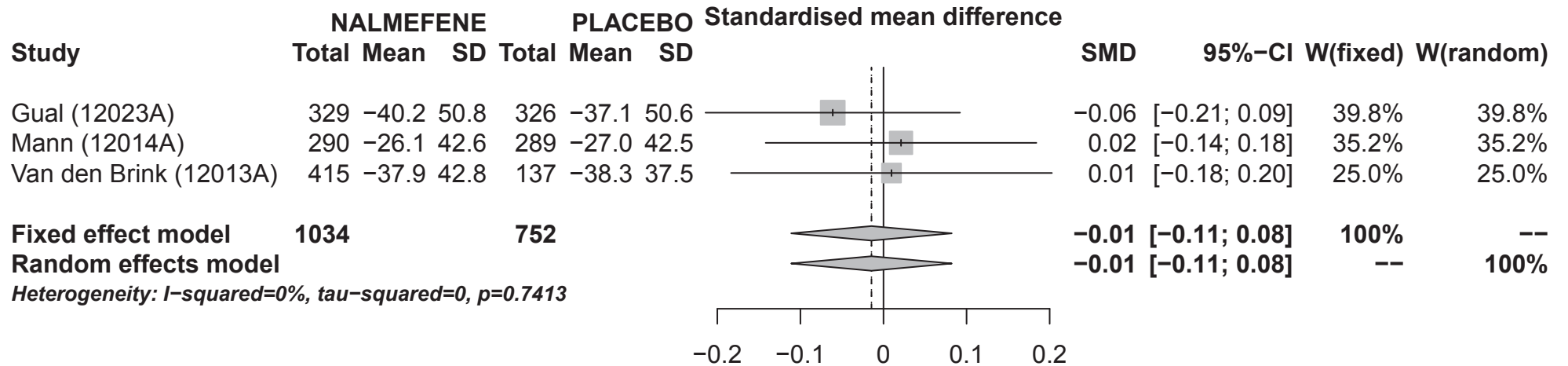
Monthly number of HDDs (BOCF) at 6 months



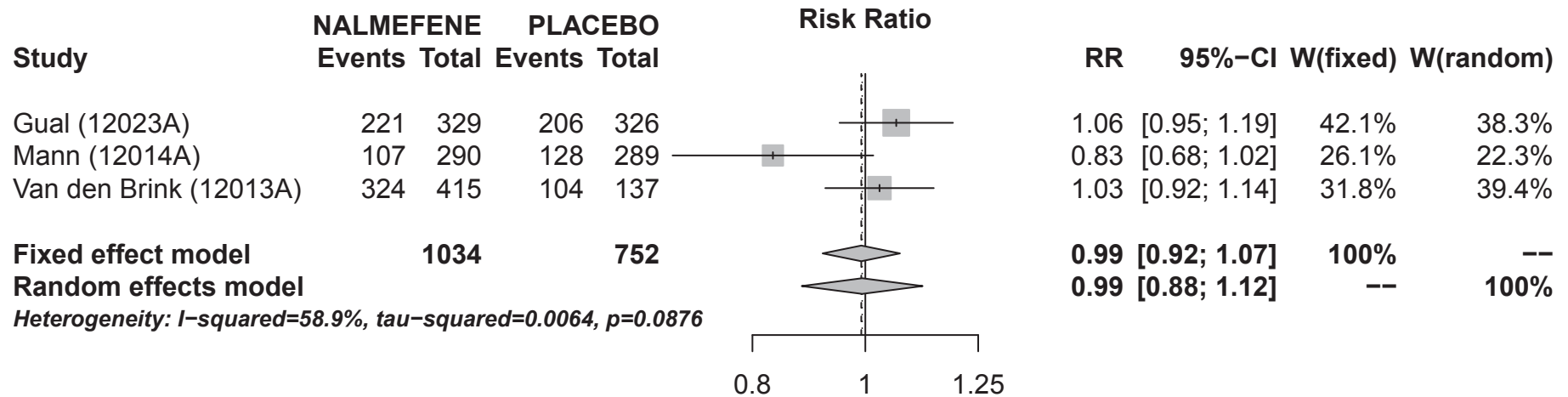
Total alcohol consumption at 6 months



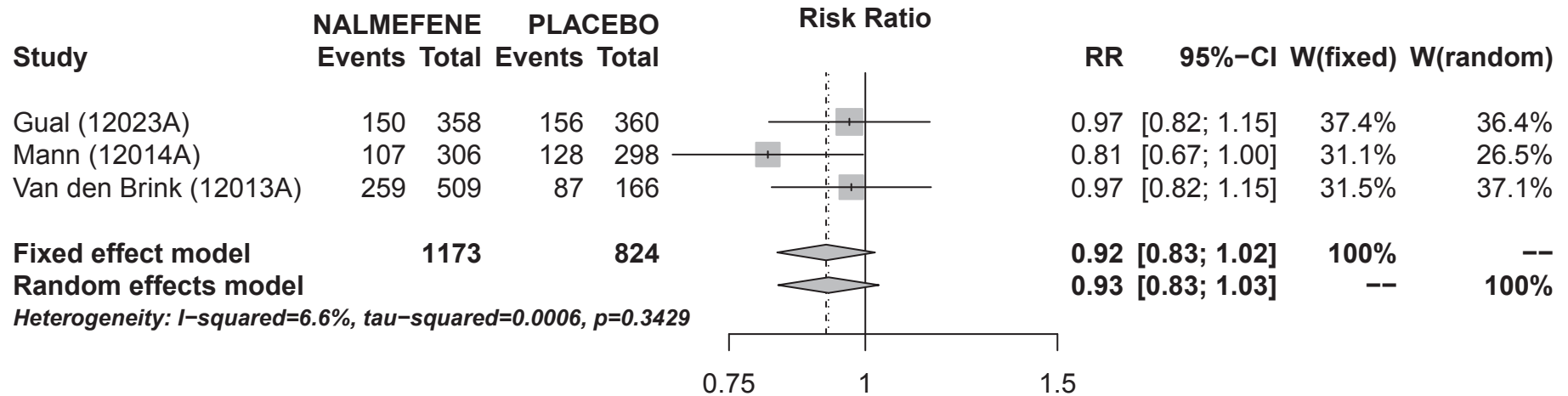
Total alcohol consumption (BOCF) at 6 months



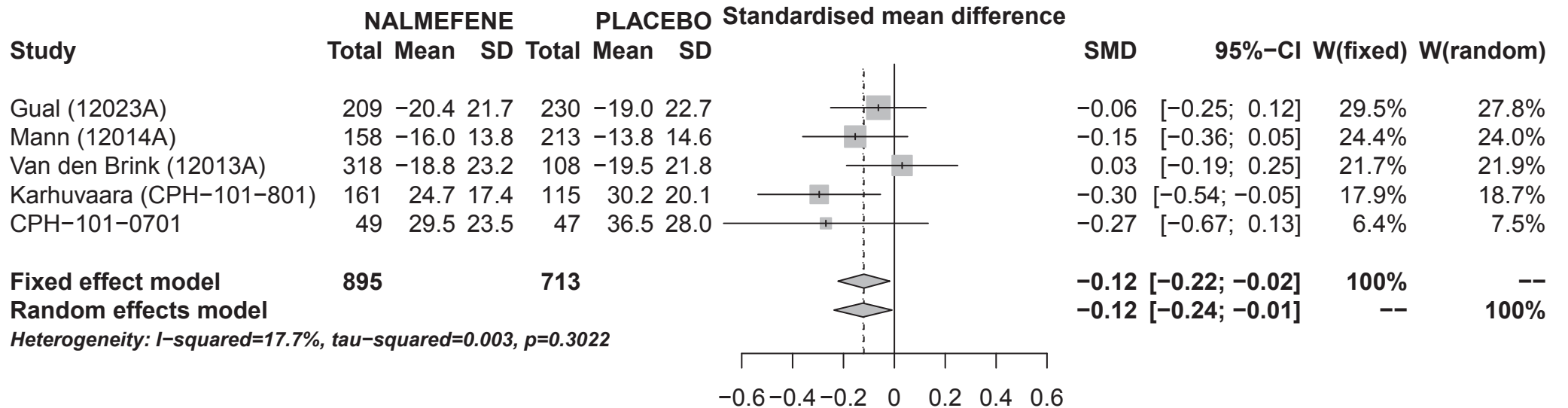
Response at 6 months



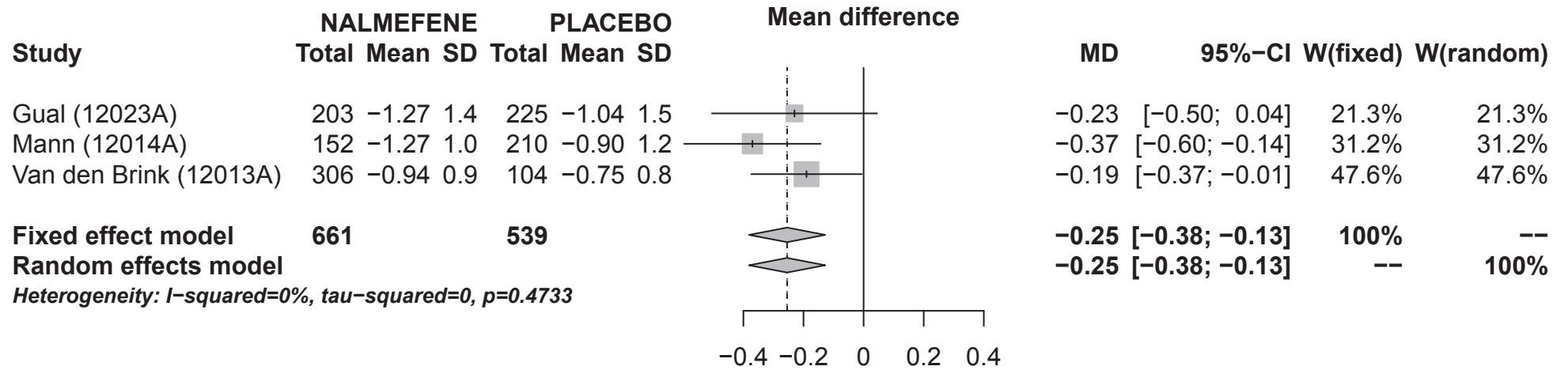
Response (LFU=F) at 6 months



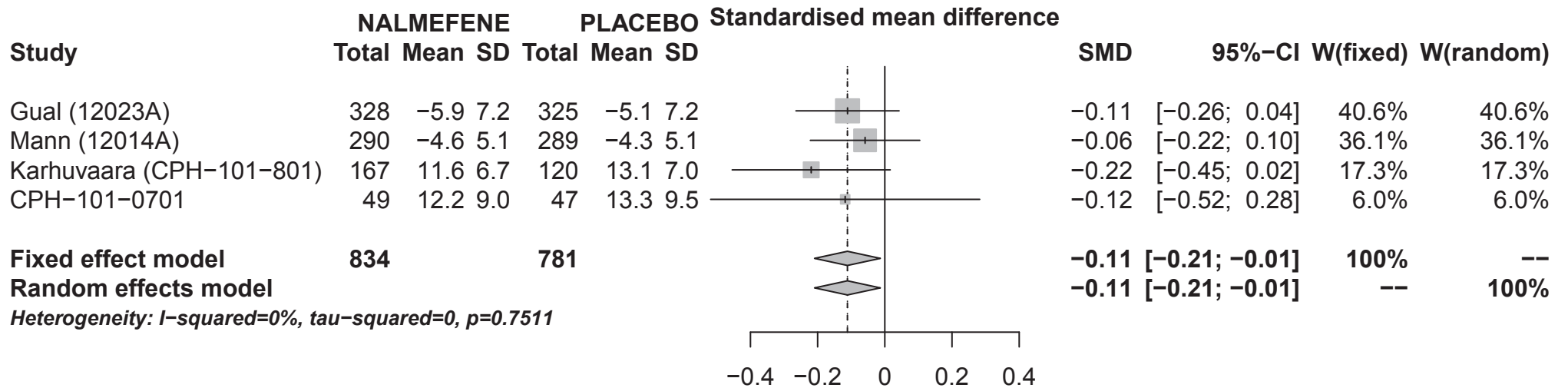
DrInC score at 6 months



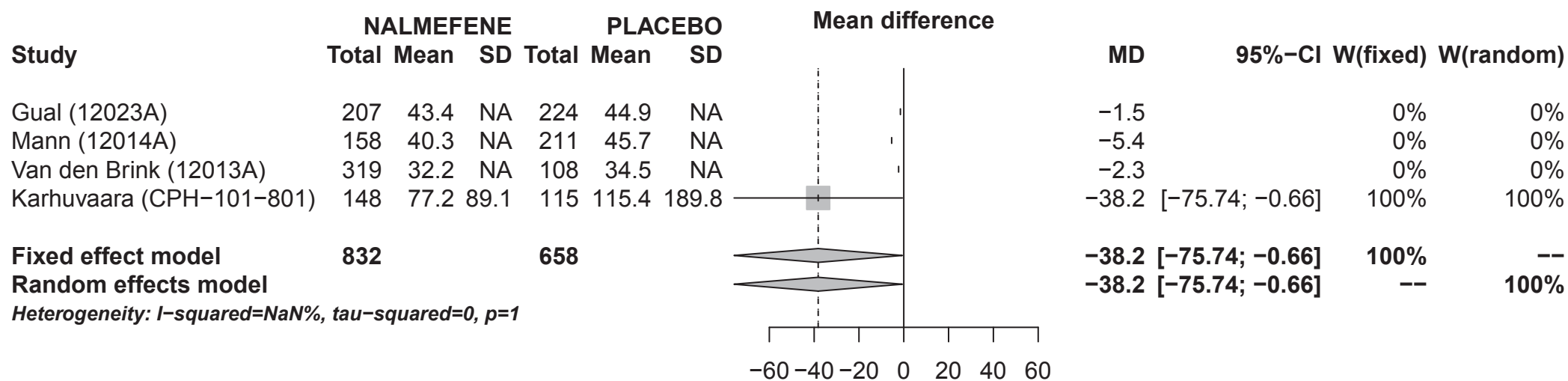
Clinical Global Impression–Severity score at 6 months



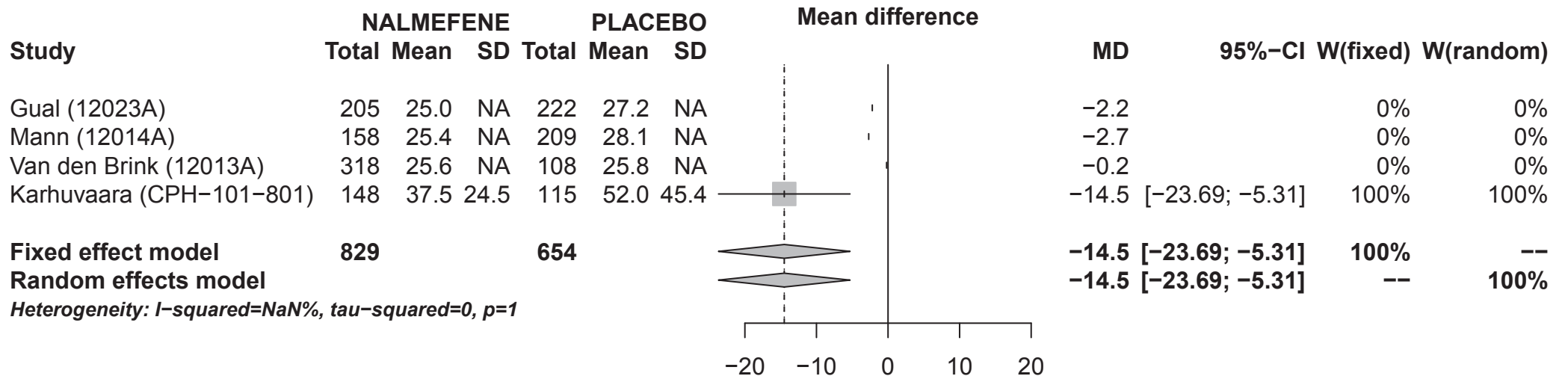
Alcohol Dependence Scale score at 6 months



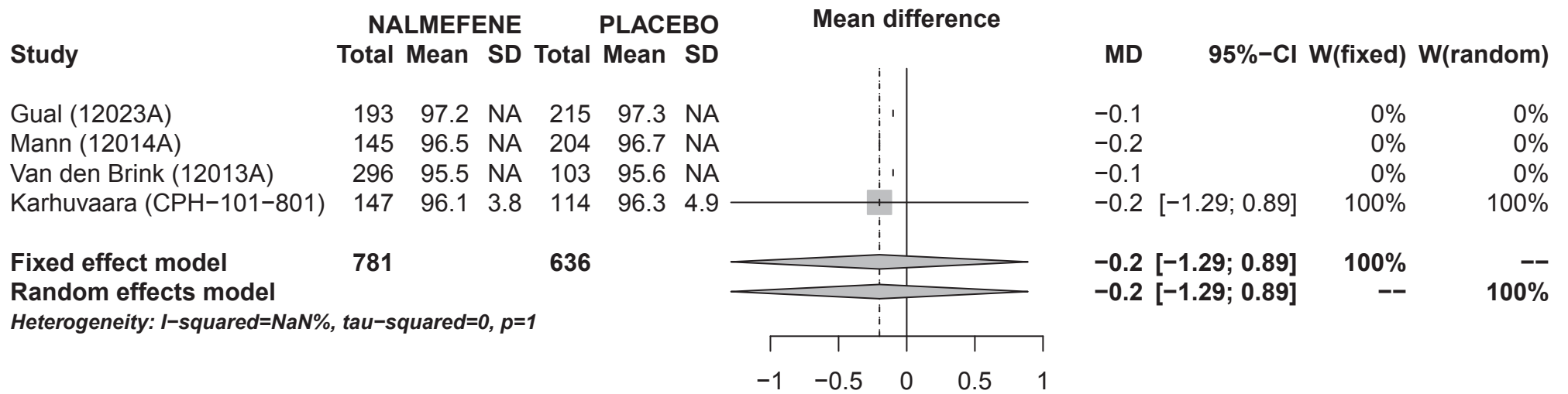
Gamma-Glutamyltransferase at 6 months



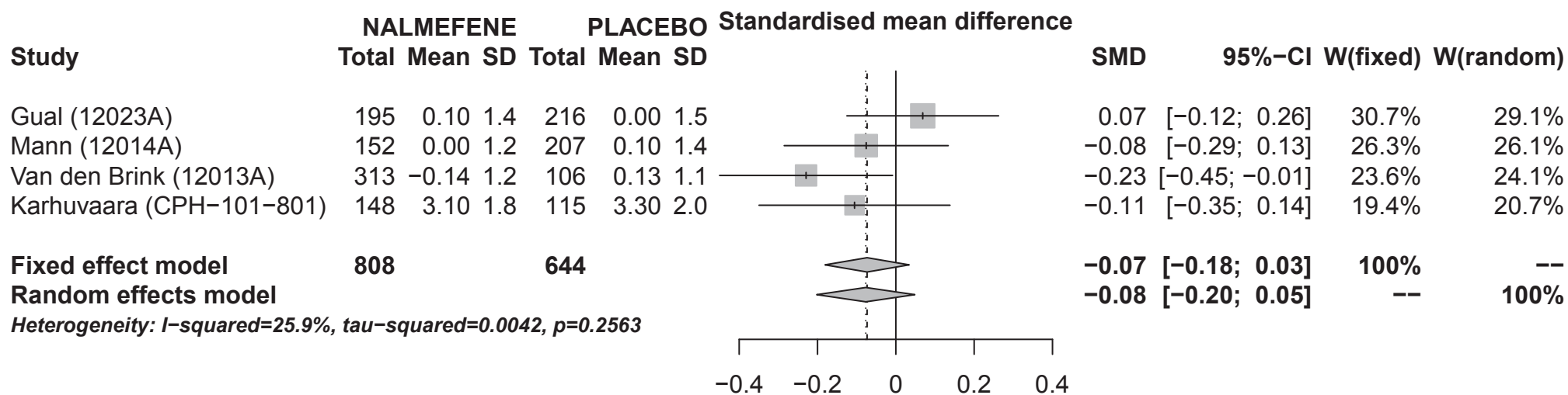
Alanine-aminotransferase at 6 months



Mean corpuscular volume at 6 months



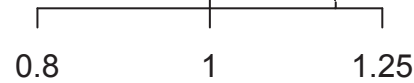
Carbohydrate-deficient transferrin at 6 months



Adverse events at 6 months

Study	NALMEFENE		PLACEBO		Risk Ratio	RR	95%-CI	W(fixed)	W(random)
	Events	Total	Events	Total					
Gual (12023A)	232	341	199	337		1.15	[1.03; 1.29]	32.2%	19.3%
Mann (12014A)	246	302	198	296		1.22	[1.11; 1.34]	32.2%	27.4%
Karhuvaara (CPH-101-801)	230	242	131	161		1.17	[1.08; 1.26]	25.3%	40.6%
CPH-101-0701	75	85	63	82		1.15	[1.00; 1.32]	10.3%	12.7%
Fixed effect model	970		876			1.18	[1.11; 1.24]	100%	--
Random effects model						1.18	[1.12; 1.24]	--	100%

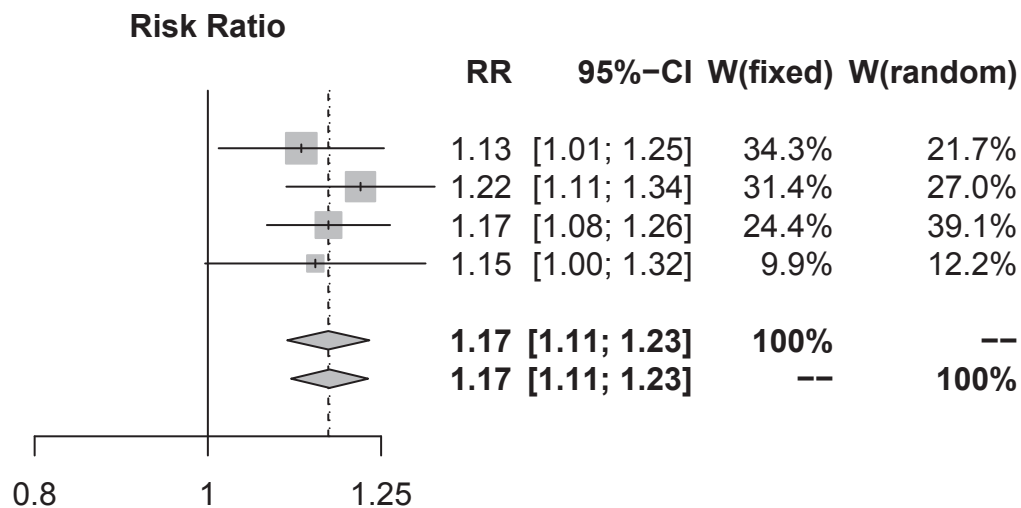
Heterogeneity: I-squared=0%, tau-squared=0, p=0.859



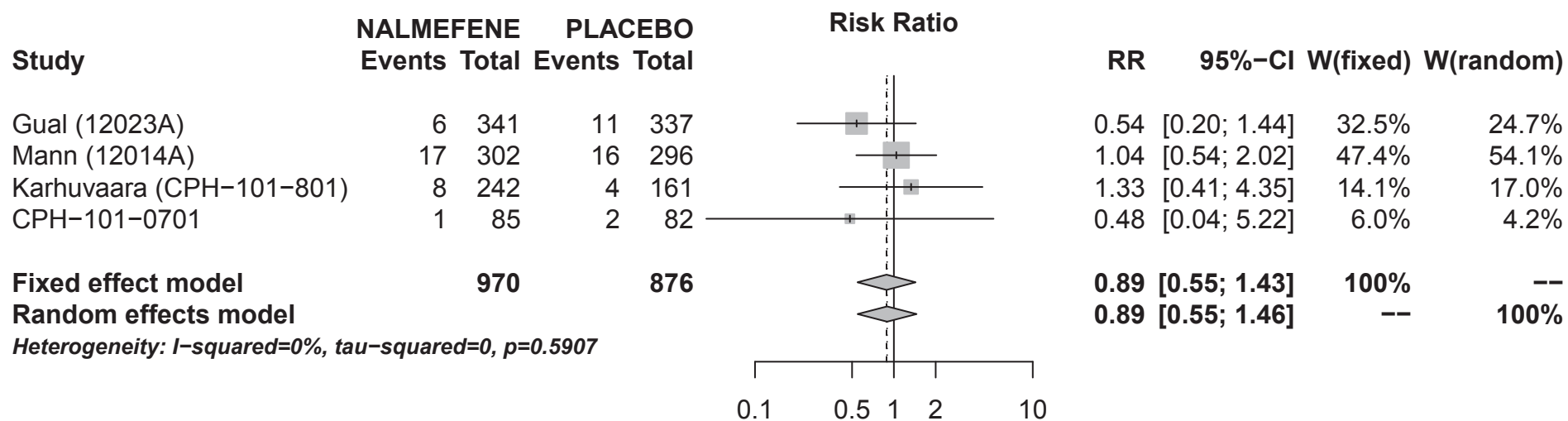
Adverse events (LFU=F) at 6 months

Study	NALMEFENE		PLACEBO		Risk Ratio	RR	95%-CI	W(fixed)	W(random)
	Events	Total	Events	Total					
Gual (12023A)	249	358	222	360		1.13	[1.01; 1.25]	34.3%	21.7%
Mann (12014A)	250	306	200	298		1.22	[1.11; 1.34]	31.4%	27.0%
Karhuvaara (CPH-101-801)	230	242	131	161		1.17	[1.08; 1.26]	24.4%	39.1%
CPH-101-0701	75	85	63	82		1.15	[1.00; 1.32]	9.9%	12.2%
Fixed effect model	991		901			1.17	[1.11; 1.23]	100%	--
Random effects model						1.17	[1.11; 1.23]	--	100%

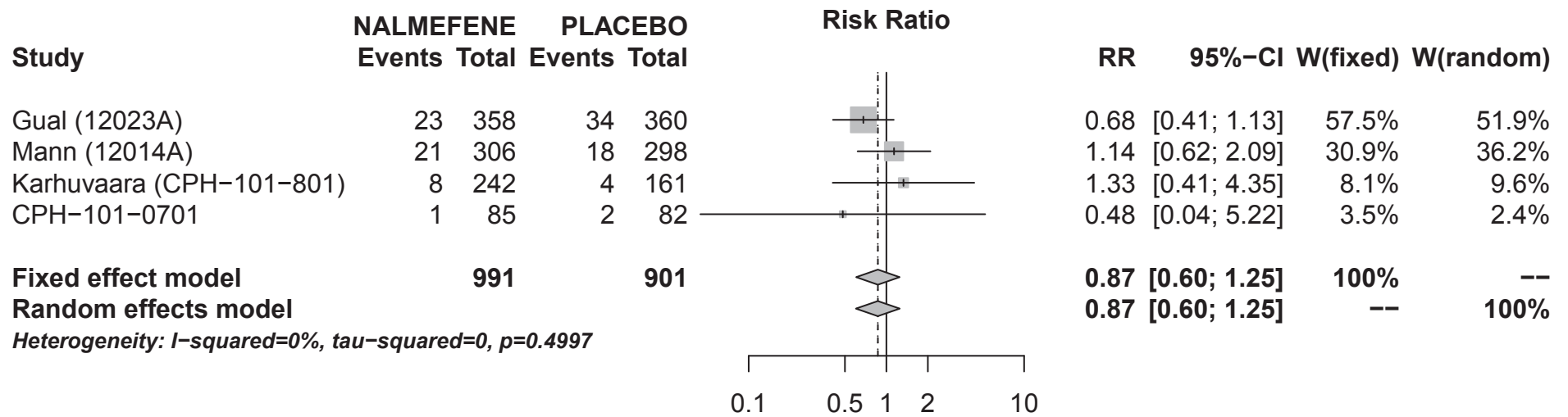
Heterogeneity: I-squared=0%, tau-squared=0, p=0.7556



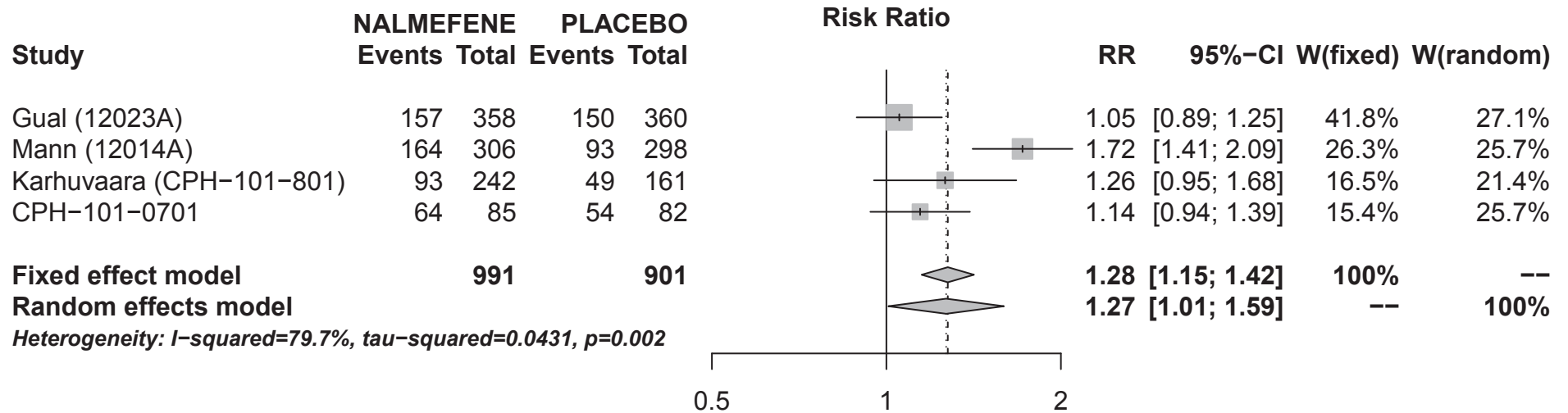
Serious adverse events at 6 months



Serious adverse events (LFU=F) at 6 months



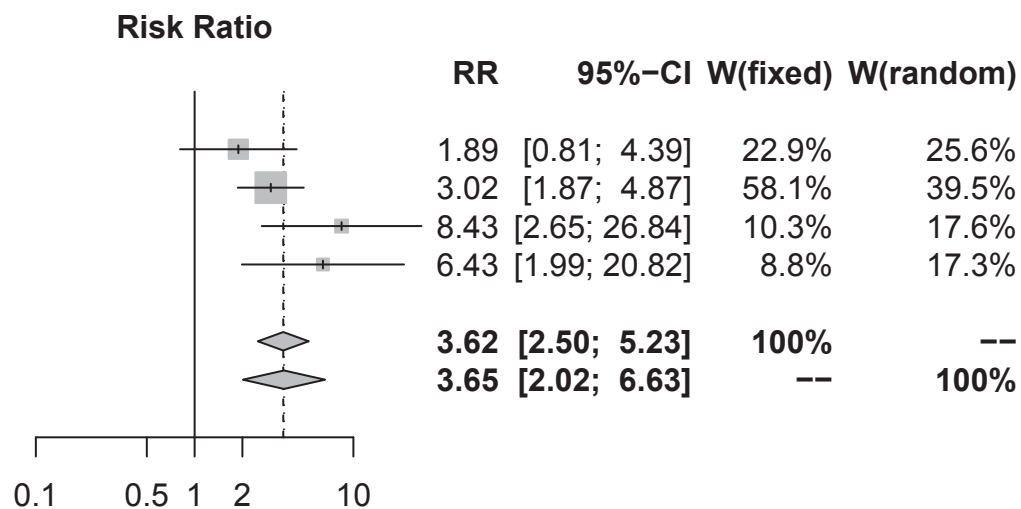
Withdrawal from the study at 6 months



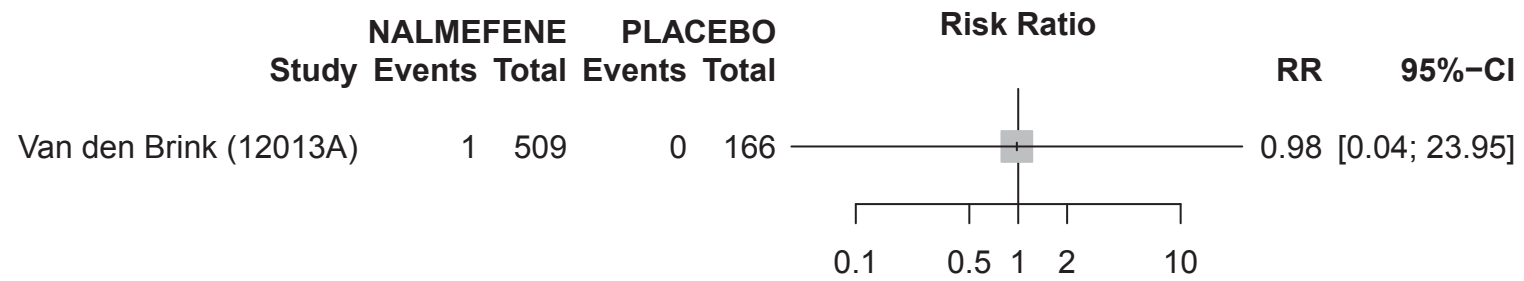
Withdrawal from the study for safety reasons at 6 months

Study	NALMEFENE		PLACEBO		Risk Ratio	RR	95%-CI	W(fixed)	W(random)
	Events	Total	Events	Total					
Gual (12023A)	15	358	8	360		1.89 [0.81; 4.39]	22.9%	25.6%	
Mann (12014A)	62	306	20	298		3.02 [1.87; 4.87]	58.1%	39.5%	
Karhuvaara (CPH-101-801)	38	242	3	161		8.43 [2.65; 26.84]	10.3%	17.6%	
CPH-101-0701	20	85	3	82		6.43 [1.99; 20.82]	8.8%	17.3%	
Fixed effect model	991		901			3.62 [2.50; 5.23]	100%	--	
Random effects model						3.65 [2.02; 6.63]	--	100%	

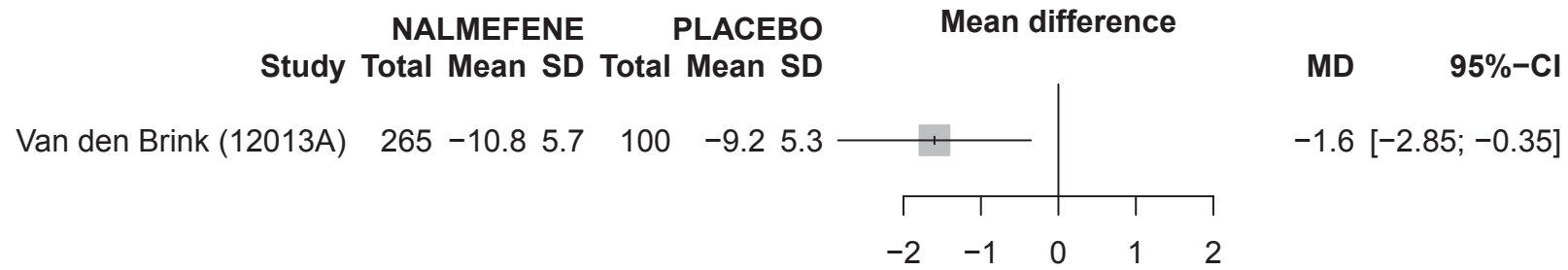
Heterogeneity: I-squared=48.3%, tau-squared=0.1742, p=0.1218



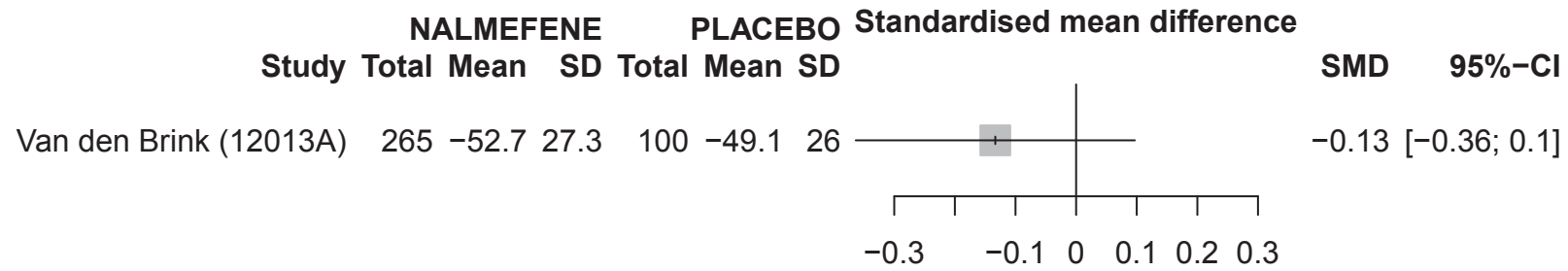
Mortality at 1 year



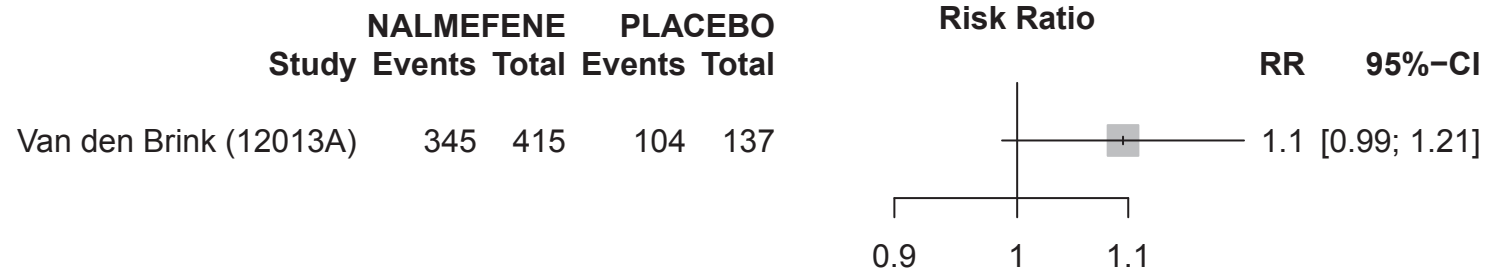
Monthly number of HDDs at 1 year



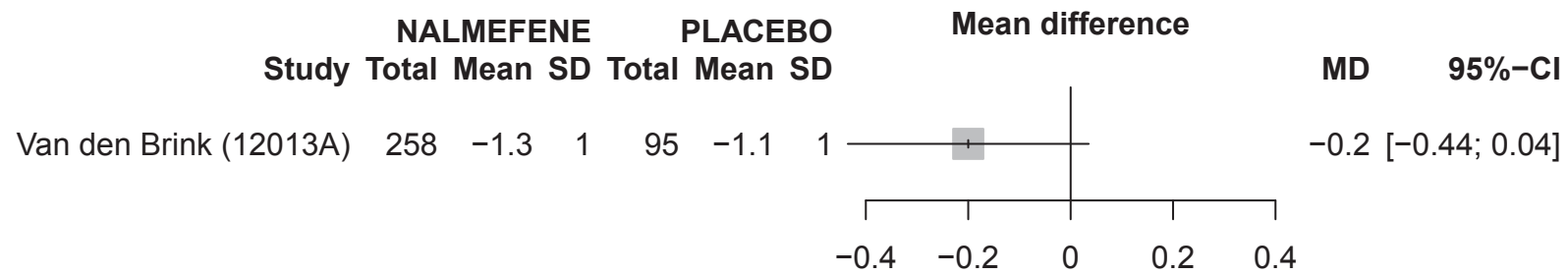
Total alcohol consumption at 1 year



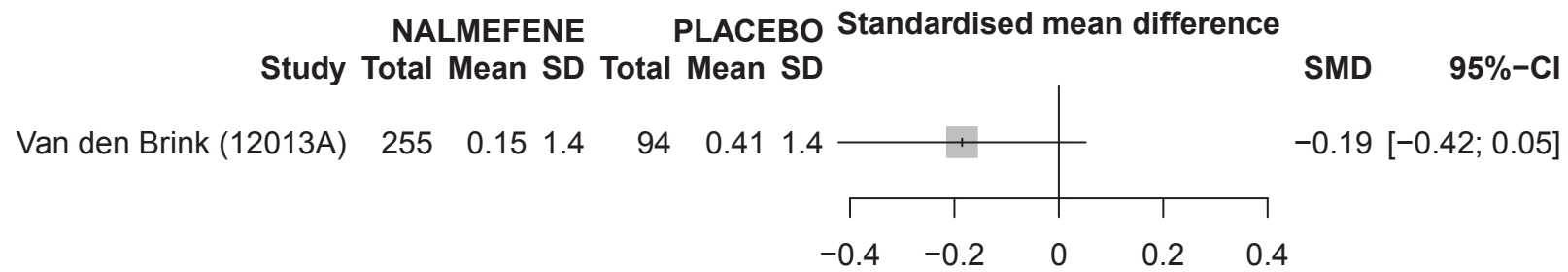
Response at 1 year



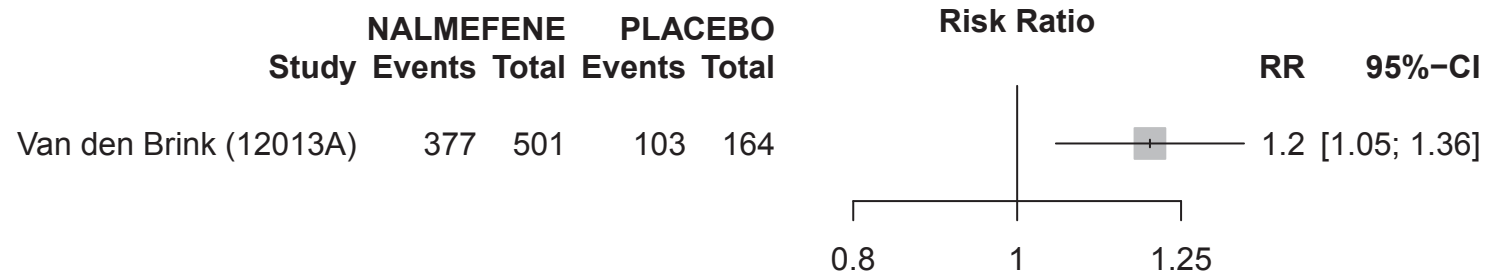
Clinical Global Impression–Severity score at 1 year



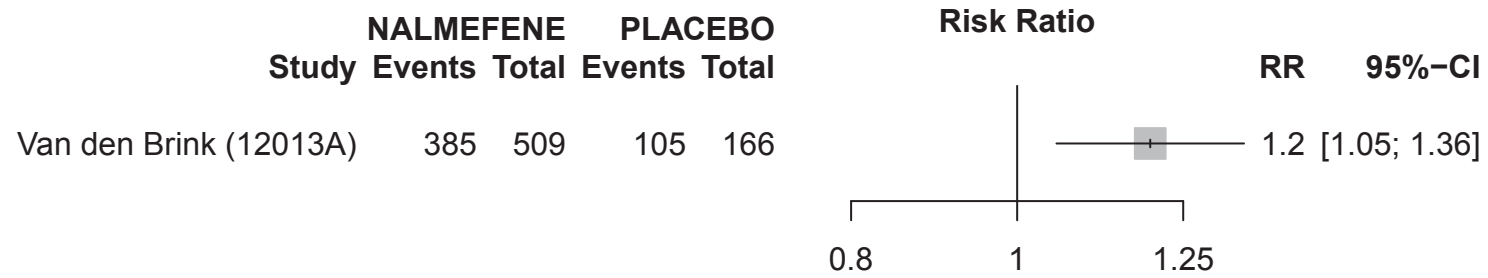
Carbohydrate-deficient transferrin at 1 year



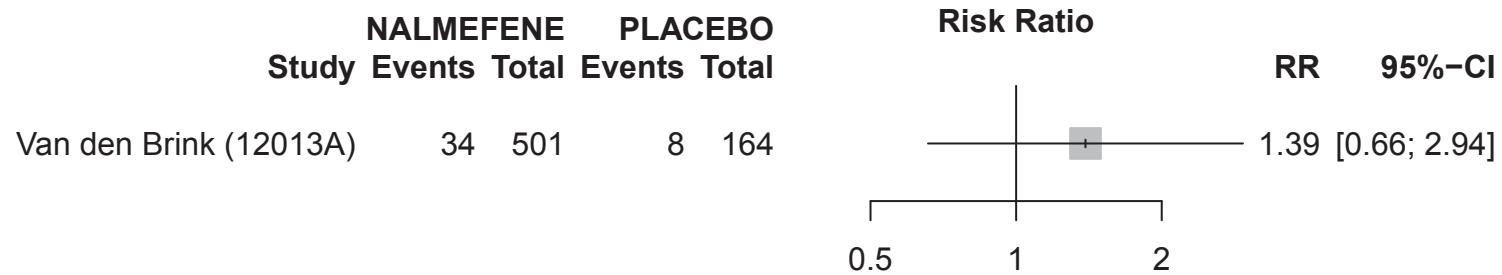
Adverse events at 1 year



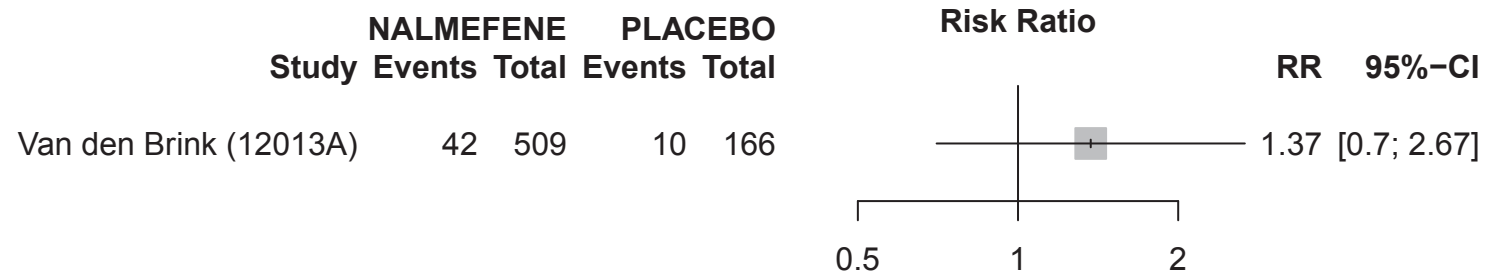
Adverse events (LFU=F) at 1 year



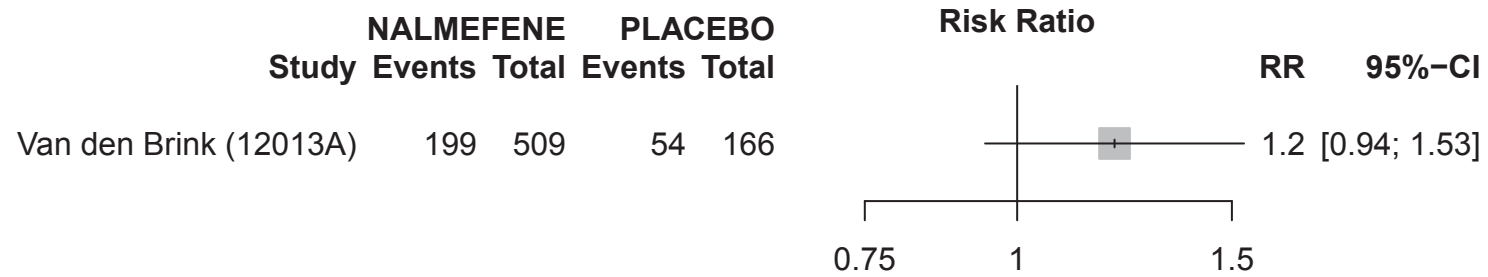
Serious adverse events at 1 year



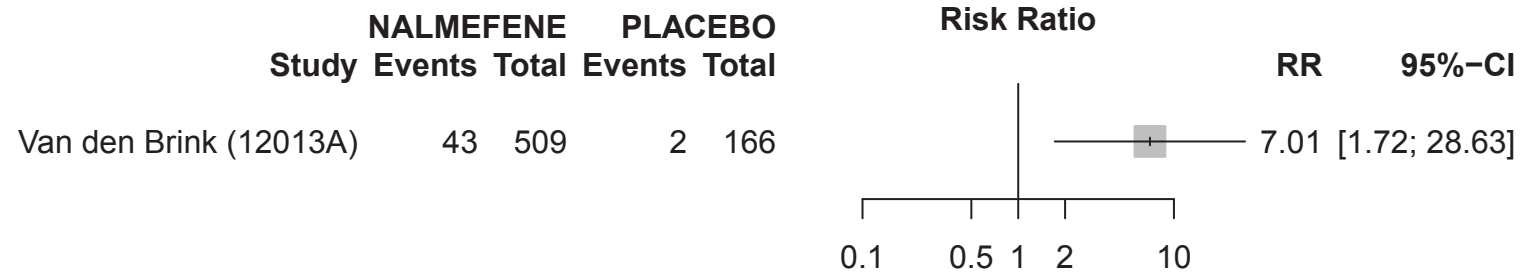
Serious adverse events (LFU=F) at 1 year



Withdrawal from the study at 1 year



Withdrawal from the study for safety reasons at 1 year



SENSITIVITY ANALYSIS

List of outcomes for which data involving studies lasting less than 6 months are available:

Health outcomes:

- Mortality ;

Alcohol consumption outcomes:

- Monthly number of HDDs ;
- Total alcohol consumption ;
- DrInC score ;
- Alcohol Dependence Scale score ;

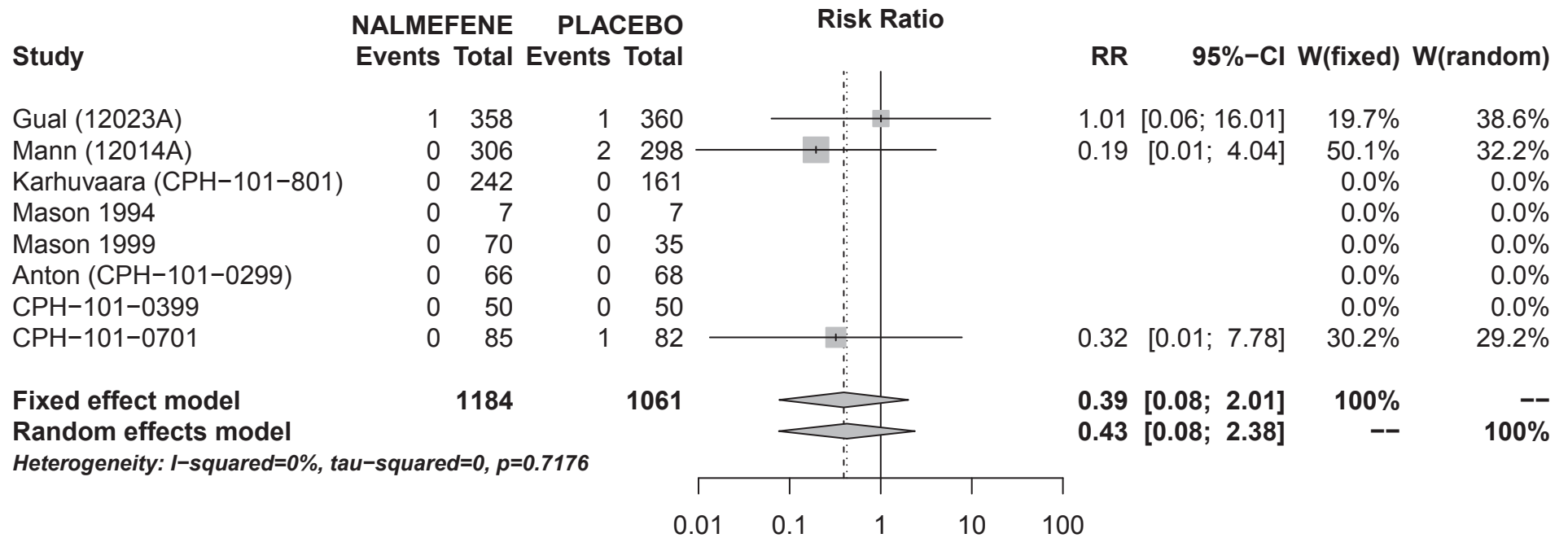
Biological outcomes:

- γ -Glutamyltransferase ;
- Alanine-aminotransferase ;
- Mean corpuscular volume ;
- Carbohydrate-deficient transferrin ;

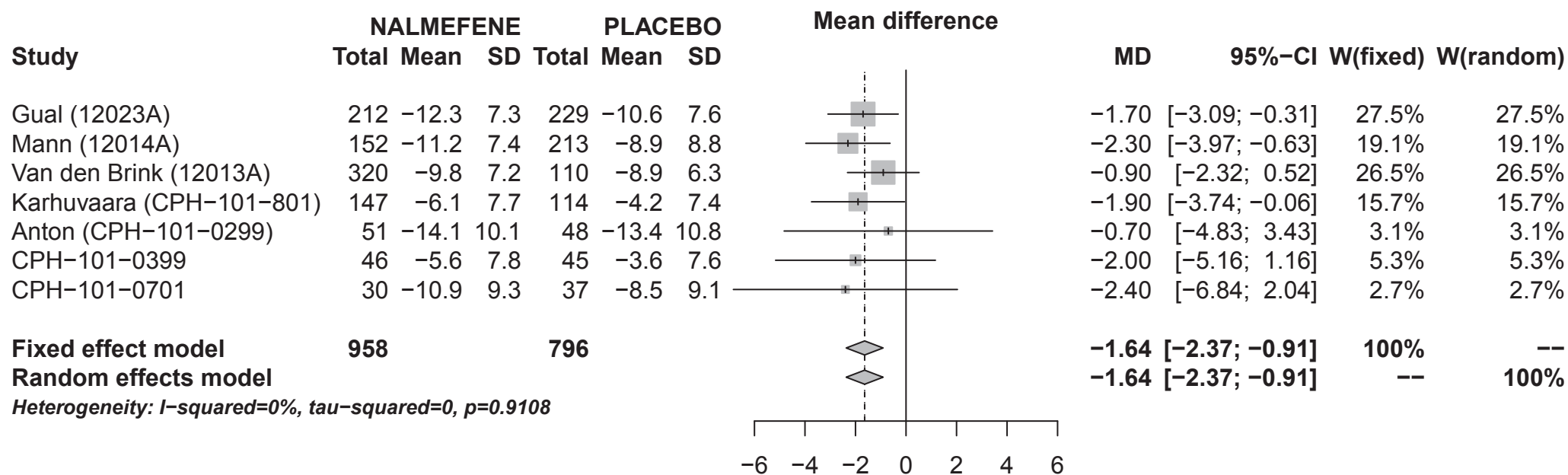
Treatment safety outcomes:

- Adverse events ;
- Serious adverse events ;
- Withdrawal from the study ;
- Withdrawal from the study for safety reasons.

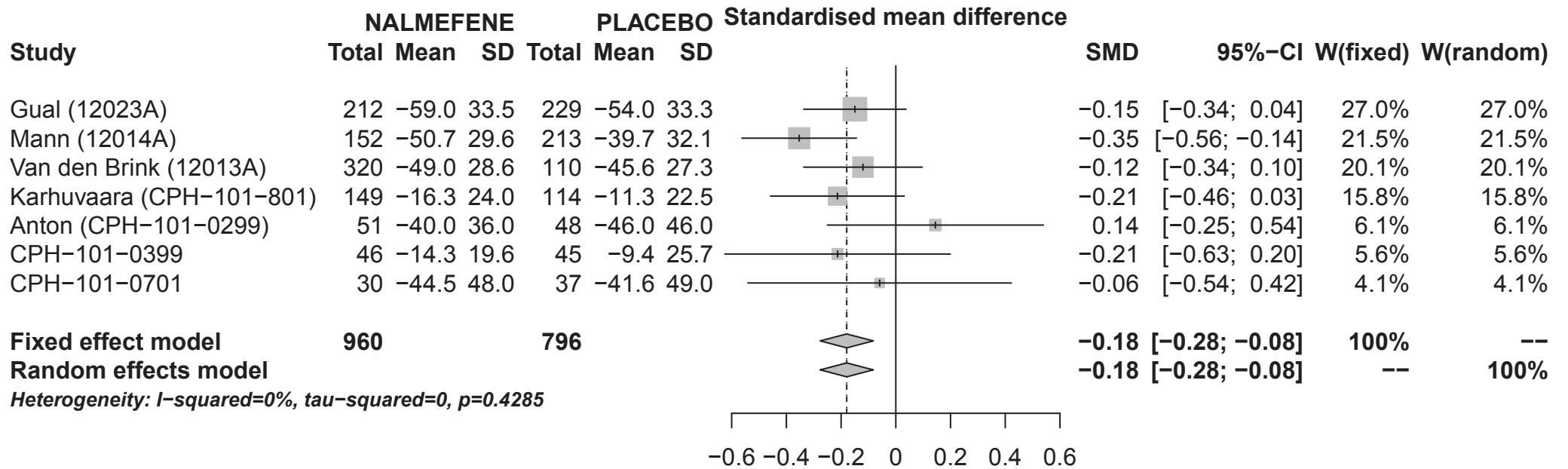
Mortality



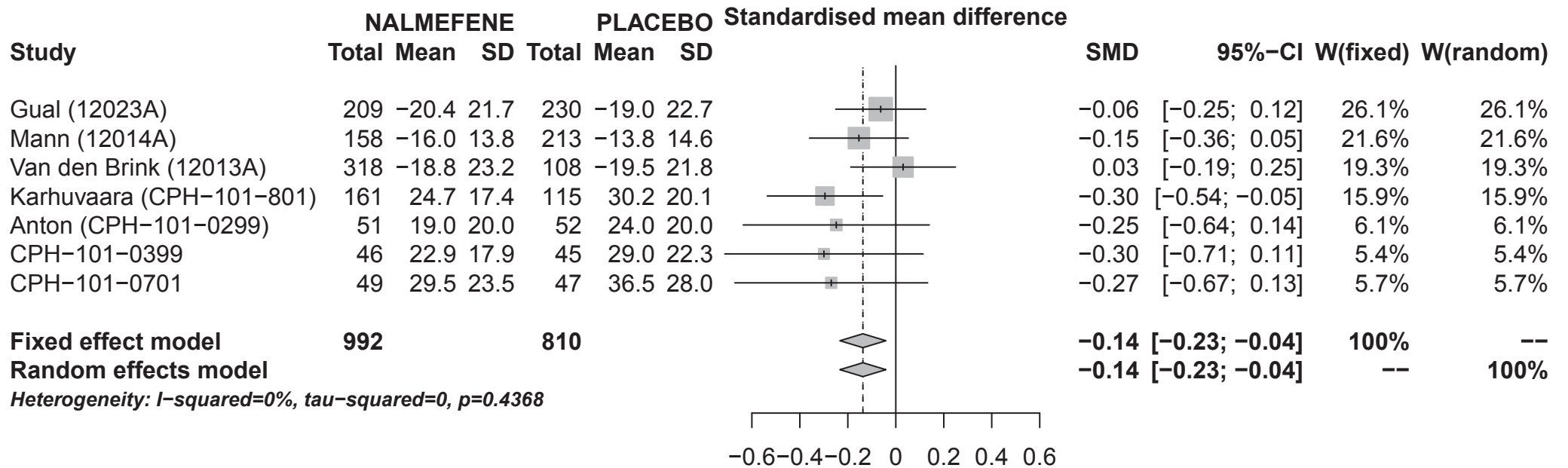
Monthly number of HDDs



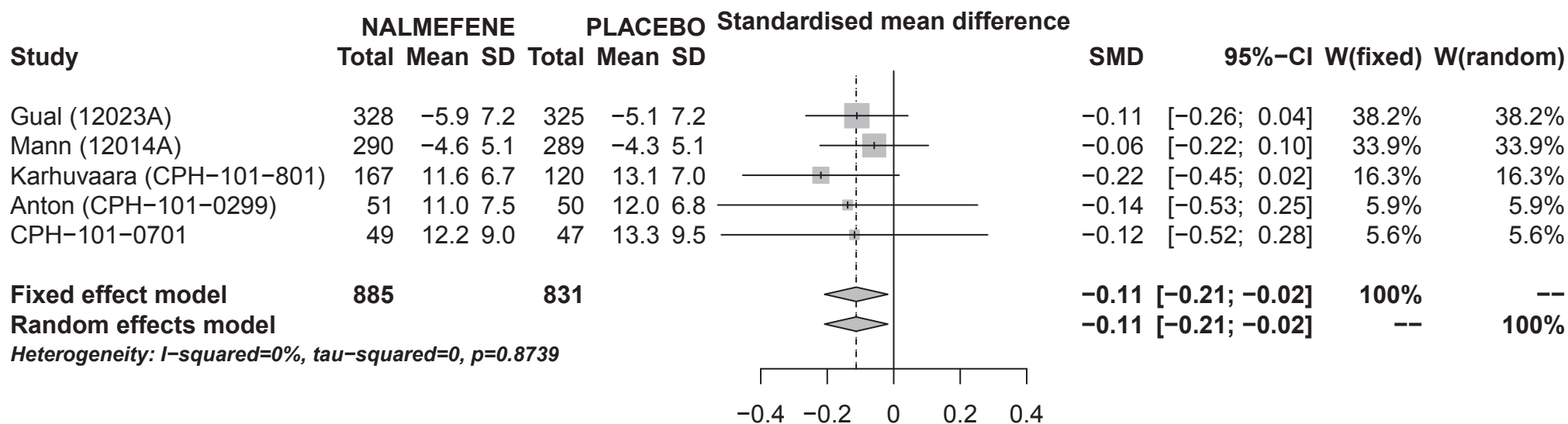
Total alcohol consumption



DrInC score

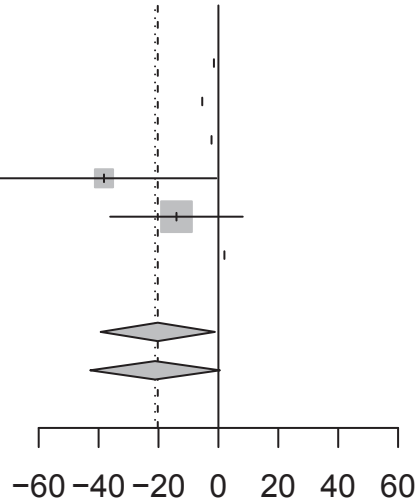


Alcohol Dependence Scale score



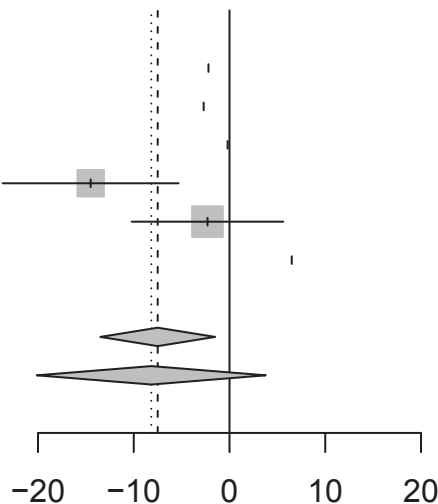
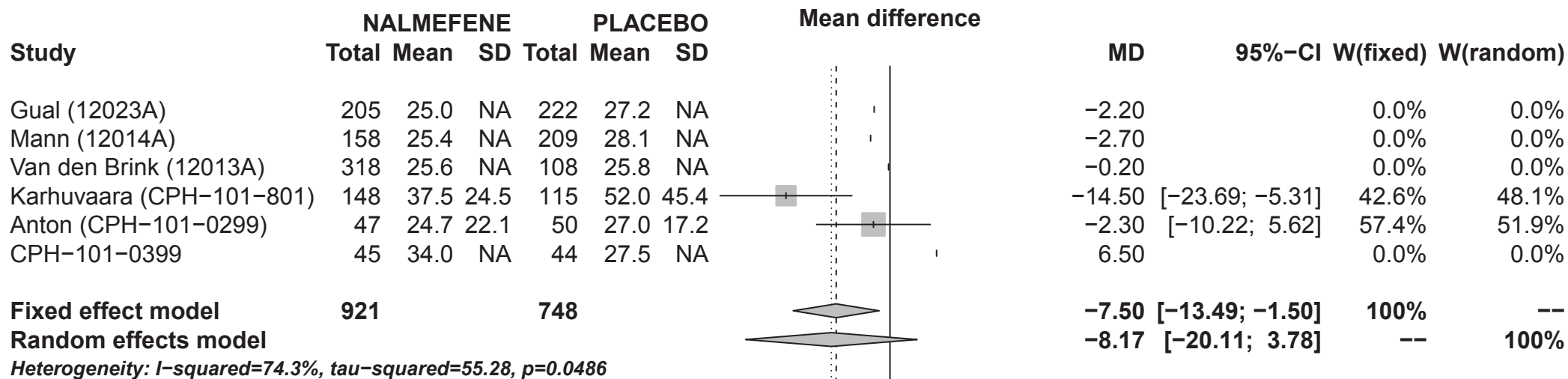
Gamma-Glutamyltransferase

Study	NALMEFENE			PLACEBO			Mean difference	MD	95%-CI	W(fixed)	W(random)
	Total	Mean	SD	Total	Mean	SD					
Gual (12023A)	207	43.4	NA	224	44.9	NA		-1.50		0.0%	0.0%
Mann (12014A)	158	40.3	NA	211	45.7	NA		-5.40		0.0%	0.0%
Van den Brink (12013A)	319	32.2	NA	108	34.5	NA		-2.30		0.0%	0.0%
Karhuvaara (CPH-101-801)	148	77.2	89.1	115	115.4	189.8		-38.20	[-75.74; -0.66]	25.8%	29.6%
Anton (CPH-101-0299)	47	44.4	46.3	50	58.4	64.0		-14.00	[-36.13; 8.13]	74.2%	70.4%
CPH-101-0399	45	55.0	NA	44	53.0	NA		2.00		0.0%	0.0%
Fixed effect model	924			752				-20.24	[-39.31; -1.18]	100%	--
Random effects model								-21.15	[-42.80; 0.49]	--	100%

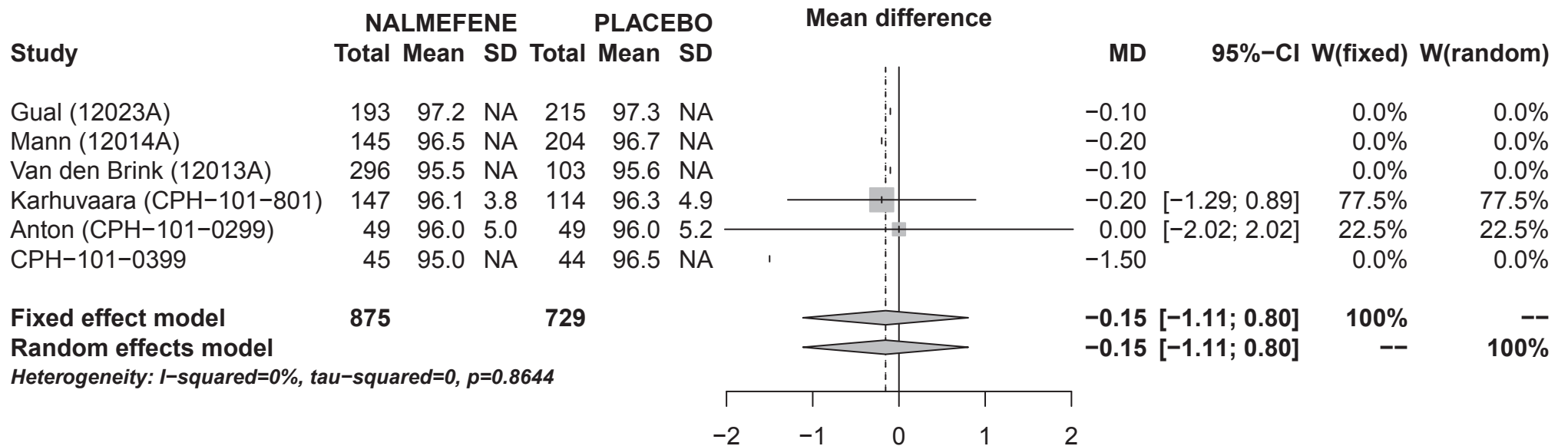


Heterogeneity: I-squared=15.6%, tau-squared=45.61, p=0.2764

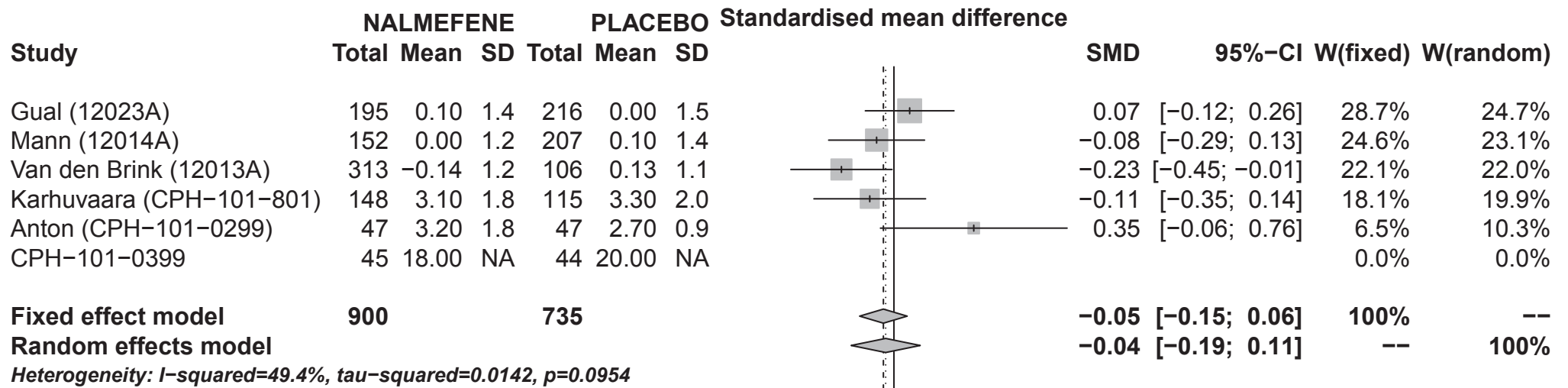
Alanine-aminotransferase



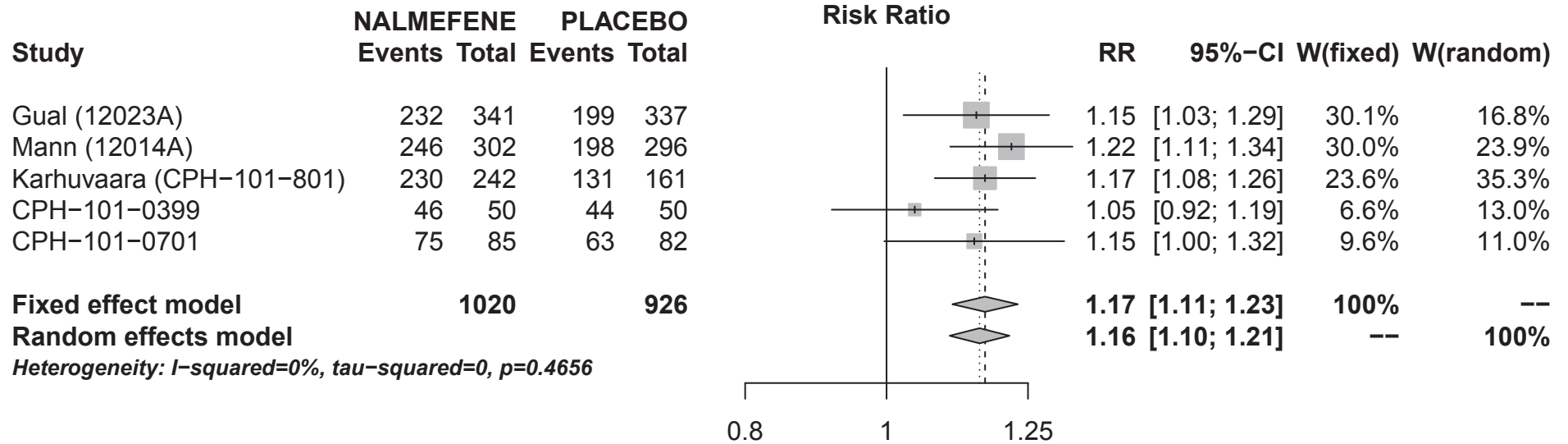
Mean corpuscular volume



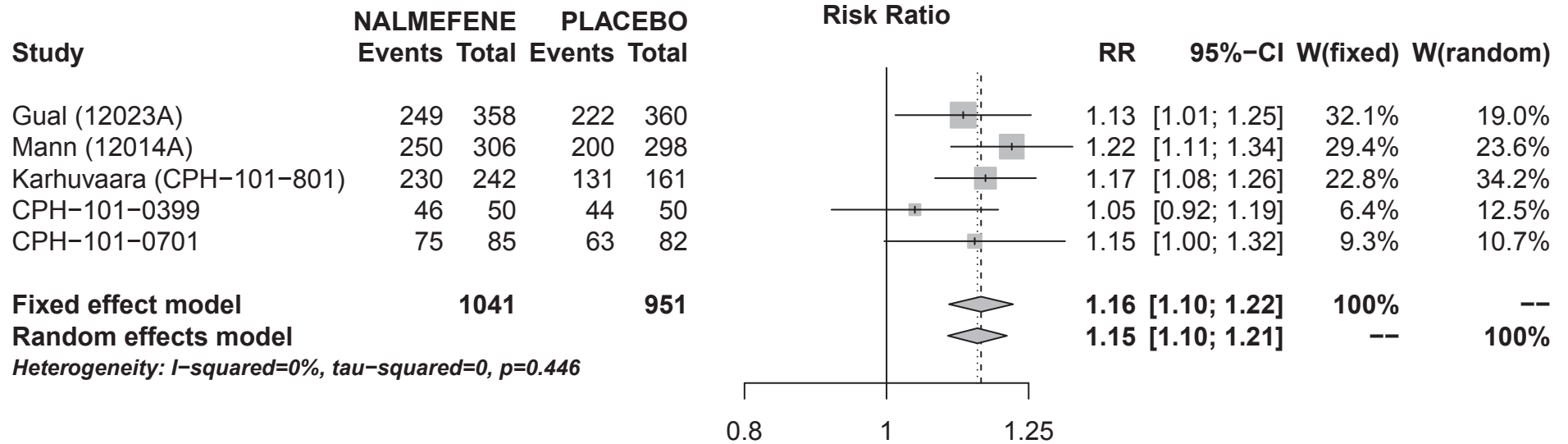
Carbohydrate-deficient transferrin



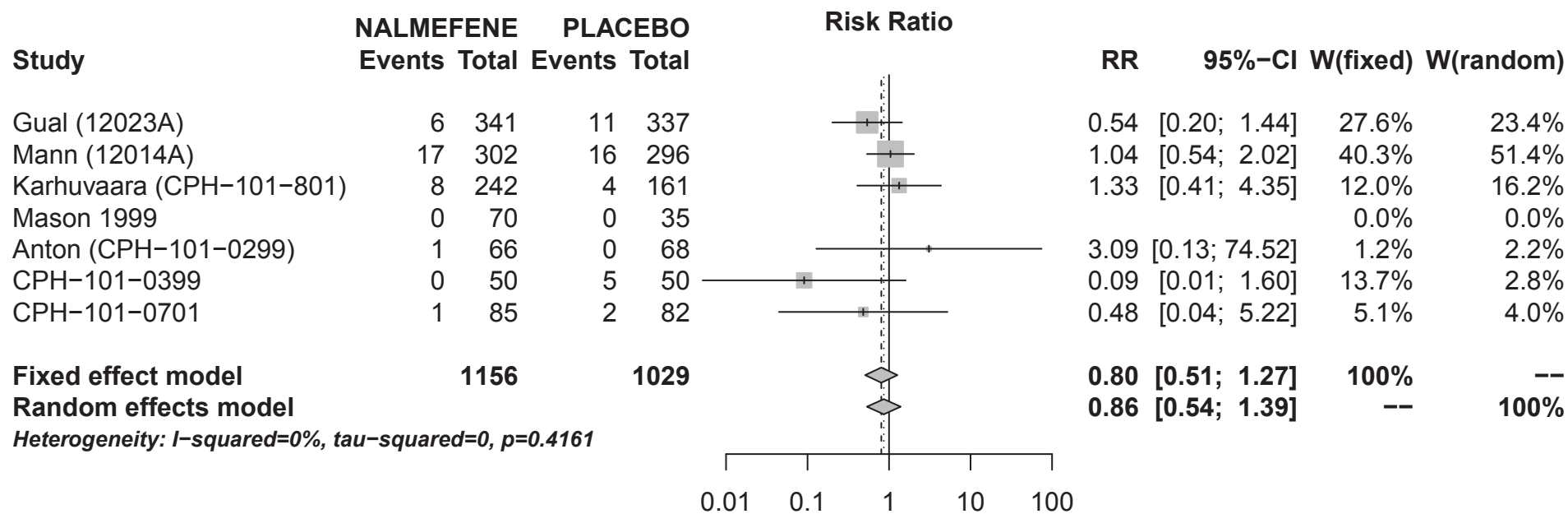
Adverse events



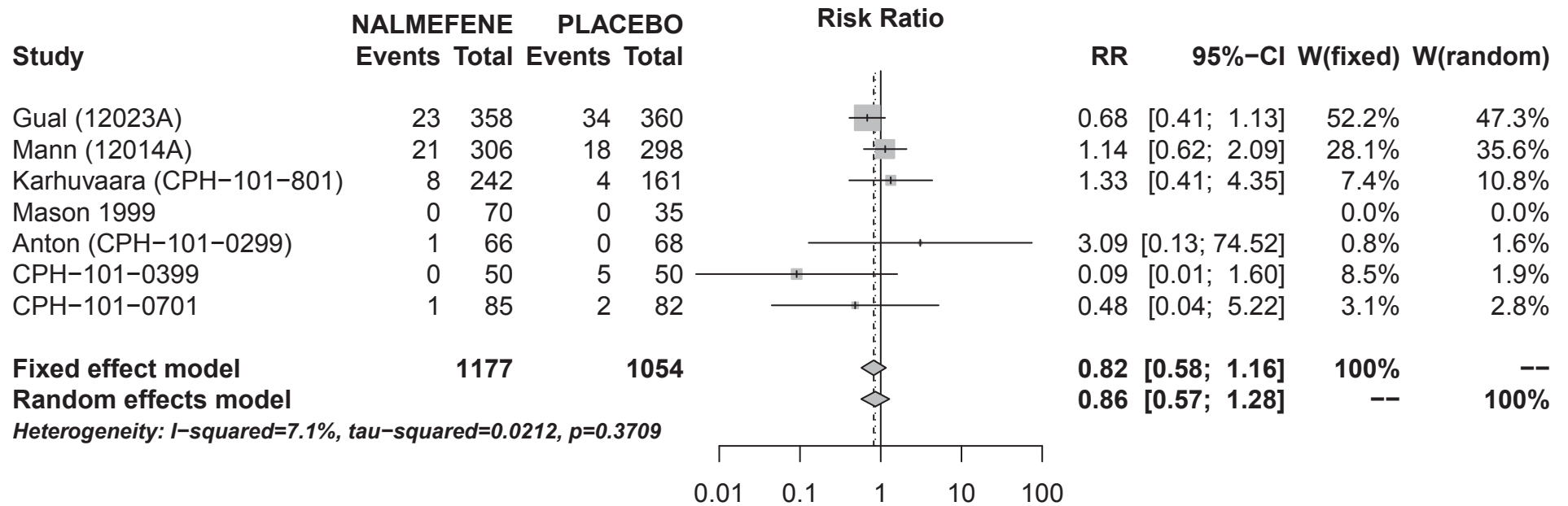
Adverse events (LFU=F)



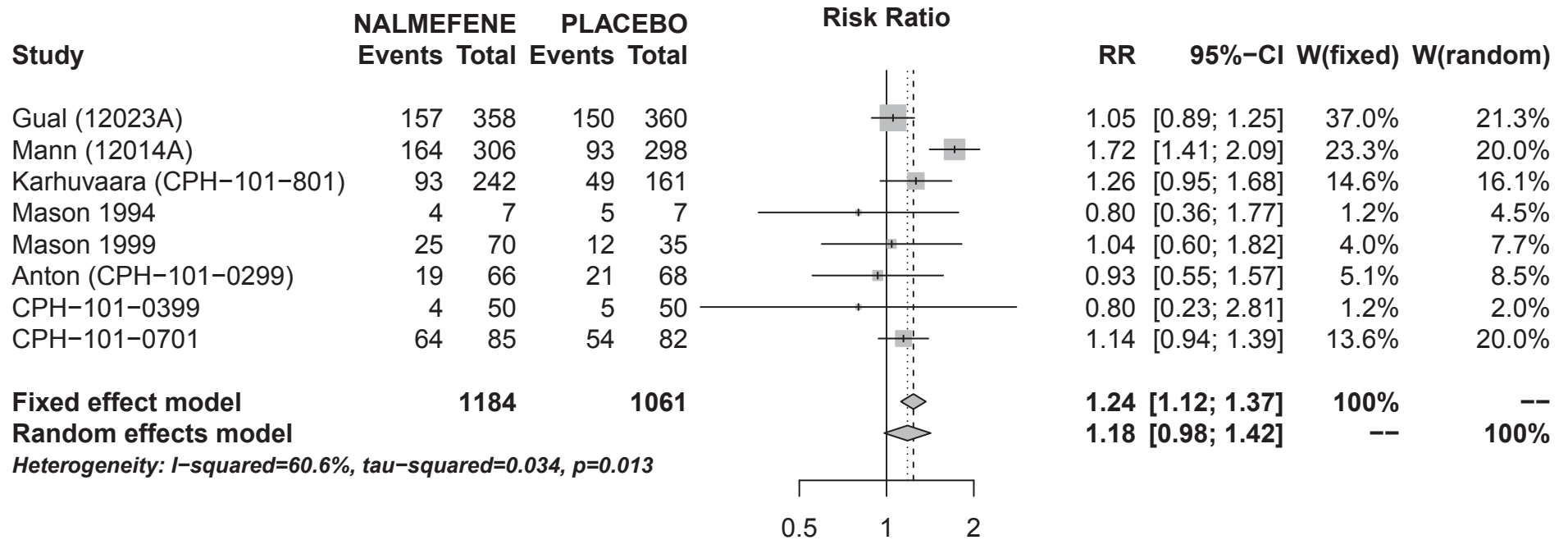
Serious adverse events



Serious adverse events (LFU=F)



Withdrawal from the study



Withdrawal from the study for safety reasons

