Longitudinal association between C-reactive protein levels and risk of psychosis: a systematic review and meta-analysis of population-based, prospective cohort studies

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Supplementary Tables

Supplementary Table 1: Quality assessment of included studies according to the Newcastle-Ottawa quality assessment scale for cohort studies

The Newcastle-Ottawa Scale (NOS) considers study quality based on three domains: 1) Quality of subject '**selection**' (representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, demonstration that outcome of interest was not present at start of study, **maximum 4 points**); 2) Quality of '**comparability**' (study controls for most important factor and any additional factor, **maximum 2 points**); 3) Quality of '**outcome**' (including assessment of outcome, length of follow-up, adequacy of follow-up, **maximum 3 points**). A maximum of 9 points was therefore considered.

Thresholds for converting NOS rating to Agency for Healthcare Research and Quality standards (good, fair, poor) (Pillinger et al., 2019). *Good – 3 or 4 stars in Selection AND 1 or 2 in Comparability AND 2 or 3 in Outcome. Fair – 2 stars in Selection AND 1 or 2 in Comparability AND 2 or 3 in Outcome. Poor – 0 or 1 stars in Selection OR 0 in Comparability OR 0 or 1 in Outcome.*

	Selection				Comparability	Outcome			HRQ score
	Representative-ness	Selection	Exposure	Outcome not at start	Comparable cohorts	Assessment	Follow-up length of time	Loss to follow-up	
Wium-Andersen et al, 2014	1	1	1	1	2	1	1	1	good
Metcalf et al, 2017	1	1	1	0	2	1	1	1	good
Laukkanen et al, 2018	1	1	1	1	2	1	1	1	good
Perry et al, 2021	1	1	1	0	2	1	1	0	good

Supplementary Figures

Supplementary Figure 1: PRISMA diagram of literature search

PRISMA 2009 Flow Diagram

Identification

Records identified through database searching
(n = 303)

Additional records identified through other sources (screening of references within eligible studies, unpublished studies from authors)
(n = 1)

Records after duplicates removed
(n = 248)

Screening

Records screened
(n = 248)

Records excluded
(n = 232)

Eligibility

Full-text articles assessed for eligibility
(n = 15)

Full-text articles excluded, with reasons
(n = 11)
1. Case-control (n = 5)
2. No diagnosis of psychotic disorder (UHR) (n = 1)
3. Study based on same cohort (n = 4)
4. Outcome pre-dates CRP measurement (n = 1)

Included

Studies included in quantitative synthesis/cohorts analysed (meta-analysis)
(n = 4)

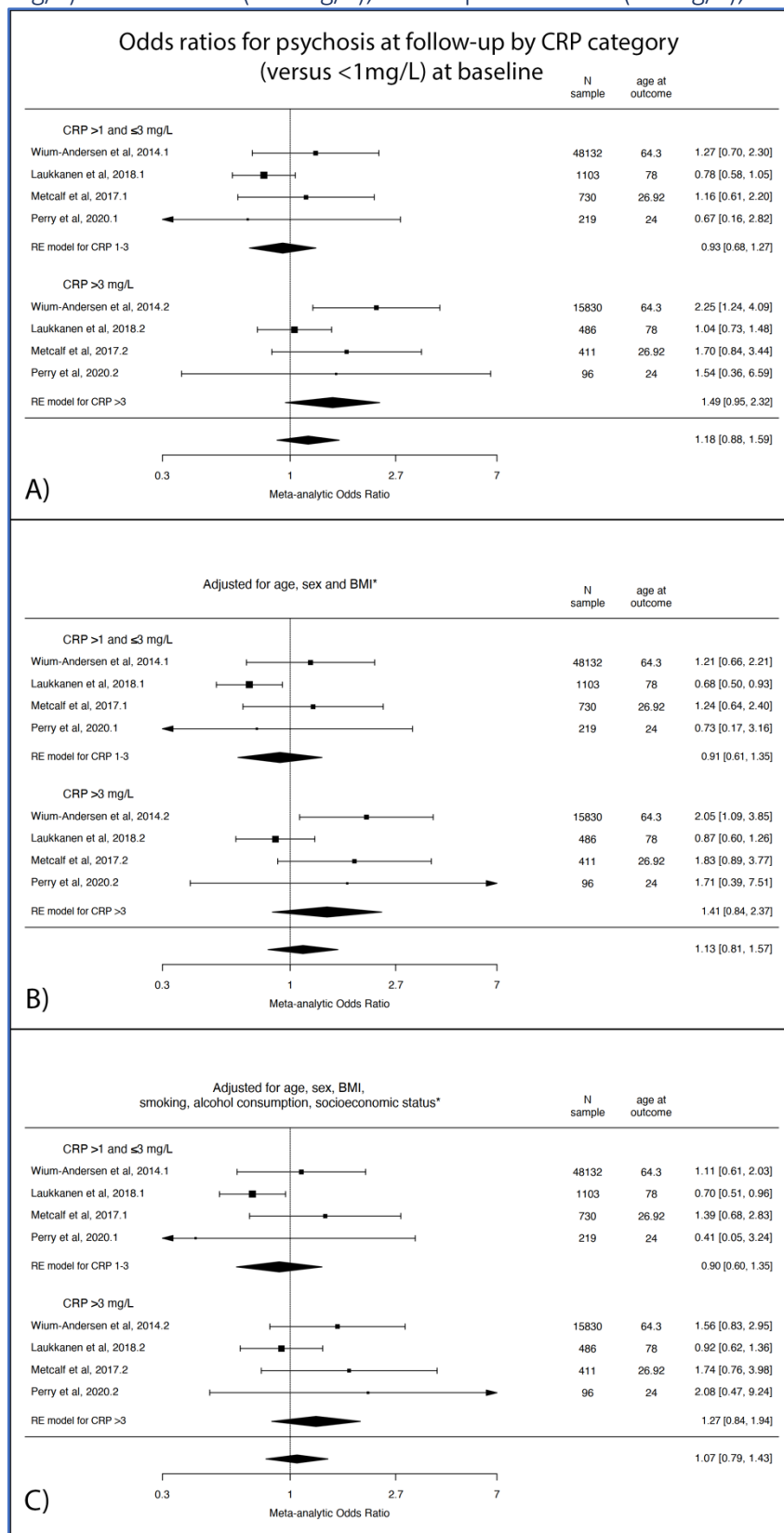*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097*

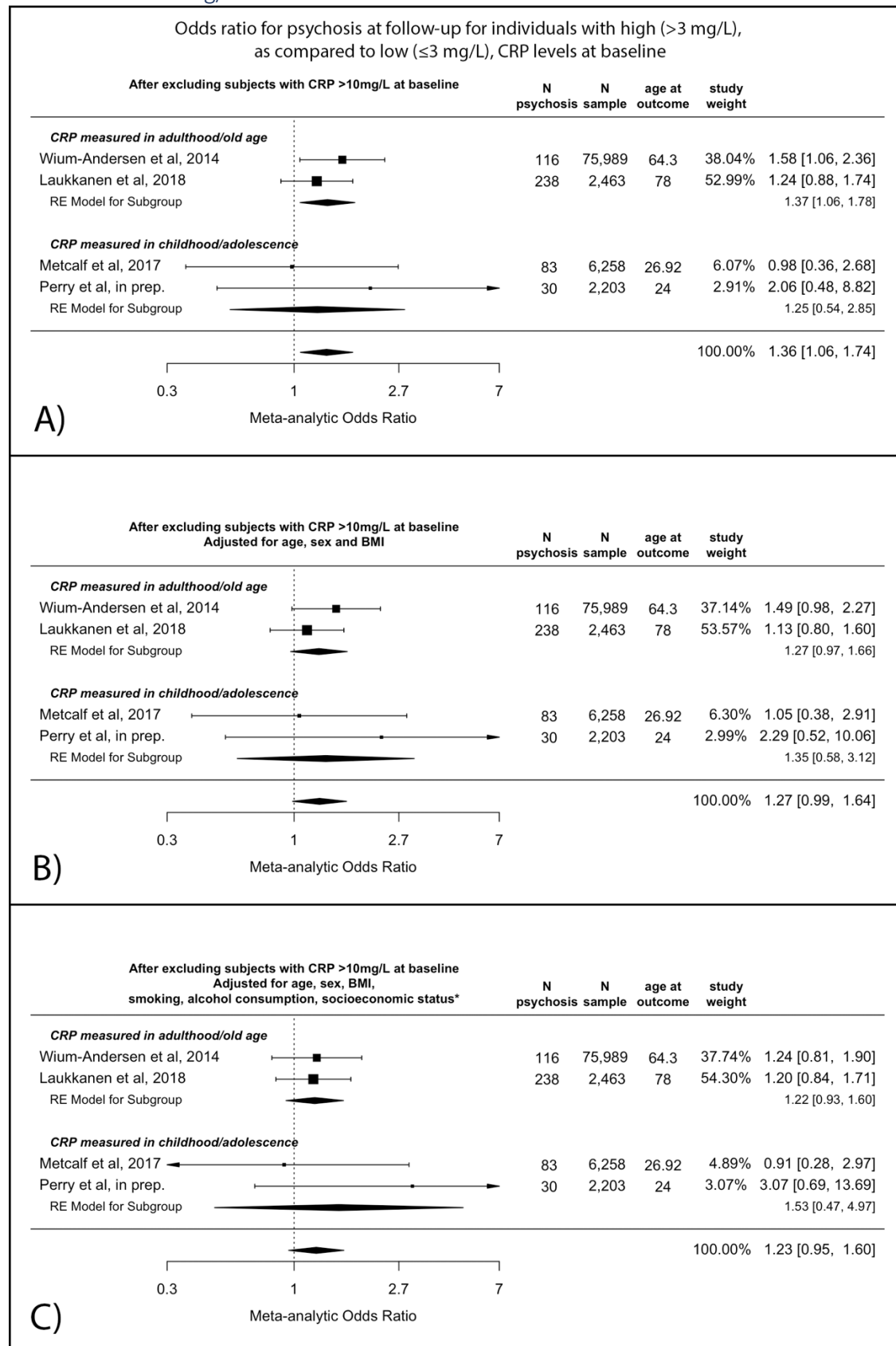**For more information, visit www.prisma-statement.org.**

CRP, C-reactive protein; UHR, ultra-high risk

BMI, body mass index; CRP, C-reactive protein; mg/L, milligrams per litre

Supplementary Figure 3: Odds ratios for psychosis at follow-up for individuals with high (>3 mg/L), as compared to low (≤3 mg/L), CRP levels at baseline – after excluding individuals with baseline CRP >10mg/L

A) Odds ratio for psychosis at follow-up for individuals with high (>3 mg/L), as compared to low (≤3 mg/L), CRP levels at baseline

After excluding subjects with CRP >10mg/L at baseline

	N psychosis	N sample	age at outcome	study weight	
CRP measured in adulthood/old age					
Wium-Andersen et al, 2014	116	75,989	64.3	38.04%	1.58 [1.06, 2.36]
Laukkanen et al, 2018	238	2,463	78	52.99%	1.24 [0.88, 1.74]
RE Model for Subgroup					1.37 [1.06, 1.78]
CRP measured in childhood/adolescence					
Metcalf et al, 2017	83	6,258	26.92	6.07%	0.98 [0.36, 2.68]
Perry et al, in prep.	30	2,203	24	2.91%	2.06 [0.48, 8.82]
RE Model for Subgroup					1.25 [0.54, 2.85]
				100.00%	1.36 [1.06, 1.74]

Meta-analytic Odds Ratio

B) After excluding subjects with CRP >10mg/L at baseline. Adjusted for age, sex and BMI

	N psychosis	N sample	age at outcome	study weight	
CRP measured in adulthood/old age					
Wium-Andersen et al, 2014	116	75,989	64.3	37.14%	1.49 [0.98, 2.27]
Laukkanen et al, 2018	238	2,463	78	53.57%	1.13 [0.80, 1.60]
RE Model for Subgroup					1.27 [0.97, 1.66]
CRP measured in childhood/adolescence					
Metcalf et al, 2017	83	6,258	26.92	6.30%	1.05 [0.38, 2.91]
Perry et al, in prep.	30	2,203	24	2.99%	2.29 [0.52, 10.06]
RE Model for Subgroup					1.35 [0.58, 3.12]
				100.00%	1.27 [0.99, 1.64]

Meta-analytic Odds Ratio

C) After excluding subjects with CRP >10mg/L at baseline. Adjusted for age, sex, BMI, smoking, alcohol consumption, socioeconomic status*

	N psychosis	N sample	age at outcome	study weight	
CRP measured in adulthood/old age					
Wium-Andersen et al, 2014	116	75,989	64.3	37.74%	1.24 [0.81, 1.90]
Laukkanen et al, 2018	238	2,463	78	54.30%	1.20 [0.84, 1.71]
RE Model for Subgroup					1.22 [0.93, 1.60]
CRP measured in childhood/adolescence					
Metcalf et al, 2017	83	6,258	26.92	4.89%	0.91 [0.28, 2.97]
Perry et al, in prep.	30	2,203	24	3.07%	3.07 [0.69, 13.69]
RE Model for Subgroup					1.53 [0.47, 4.97]
				100.00%	1.23 [0.95, 1.60]

Meta-analytic Odds Ratio

BMI, body mass index; CRP, C-reactive protein; mg/L, milligrams per litre

Odds ratios for psychosis at follow-up per SD increase in log(CRP) levels at baseline

A) After excluding subjects with CRP >10mg/L at baseline

	N psychosis	N sample	age at outcome	study weight	
CRP measured in adulthood/old age					
Wium-Andersen et al, 2014	116	75,989	64.3	28.03%	1.30 [1.08, 1.57]
Laukkanen et al, 2018	238	2,463	78	36.29%	1.00 [0.88, 1.14]
RE Model for Subgroup					1.13 [0.87, 1.46]
CRP measured in childhood/adolescence					
Metcalf et al, 2017	83	6,258	26.92	22.89%	0.97 [0.77, 1.22]
Perry et al, 2020	30	2,203	24	12.79%	0.98 [0.68, 1.41]
RE Model for Subgroup					0.97 [0.80, 1.18]
				100.00%	1.07 [0.92, 1.24]

Meta-analytic Odds Ratio

B) After excluding subjects with CRP >10mg/L at baseline
Adjusted for age, sex and BMI

	N psychosis	N sample	age at outcome	study weight	
CRP measured in adulthood/old age					
Wium-Andersen et al, 2014	116	75,989	64.3	28.45%	1.28 [1.05, 1.57]
Laukkanen et al, 2018	238	2,463	78	35.18%	0.92 [0.79, 1.07]
RE Model for Subgroup					1.08 [0.78, 1.49]
CRP measured in childhood/adolescence					
Metcalf et al, 2017	83	6,258	26.92	23.37%	1.00 [0.78, 1.29]
Perry et al, 2020	30	2,203	24	13.00%	1.00 [0.67, 1.50]
RE Model for Subgroup					1.00 [0.81, 1.24]
				100.00%	1.04 [0.88, 1.24]

Meta-analytic Odds Ratio

C) After excluding subjects with CRP >10mg/L at baseline
Adjusted for age, sex, BMI,
smoking, alcohol consumption, socioeconomic status*

	N psychosis	N sample	age at outcome	study weight	
CRP measured in adulthood/old age					
Wium-Andersen et al, 2014	116	75,989	64.3	29.31%	1.15 [0.94, 1.41]
Laukkanen et al, 2018	238	2,463	78	45.91%	0.93 [0.80, 1.08]
RE Model for Subgroup					1.02 [0.83, 1.26]
CRP measured in childhood/adolescence					
Metcalf et al, 2017	83	6,258	26.92	16.98%	0.96 [0.72, 1.28]
Perry et al, 2020	30	2,203	24	7.80%	0.96 [0.62, 1.49]
RE Model for Subgroup					0.96 [0.75, 1.22]
				100.00%	1.00 [0.88, 1.13]

Meta-analytic Odds Ratio

BMI, body mass index; CRP, C-reactive protein; mg/L, milligrams per litre

Supplementary Figure 5: Odds ratios for psychosis at follow-up for individuals with high (>3 mg/L) and medium (1-3 mg/L), as compared to low (<1 mg/L), CRP levels at baseline – after excluding individuals with baseline CRP >10mg/L
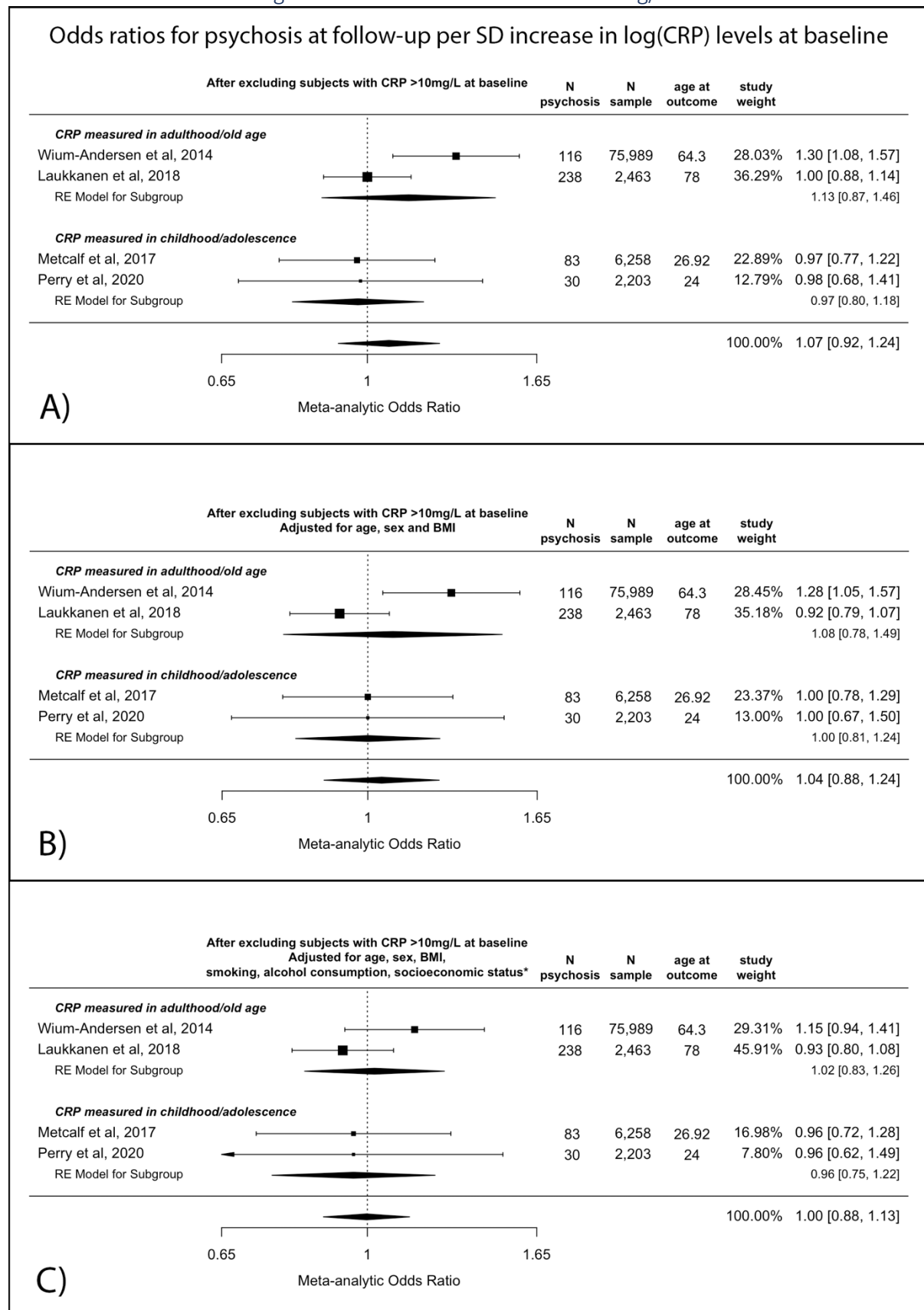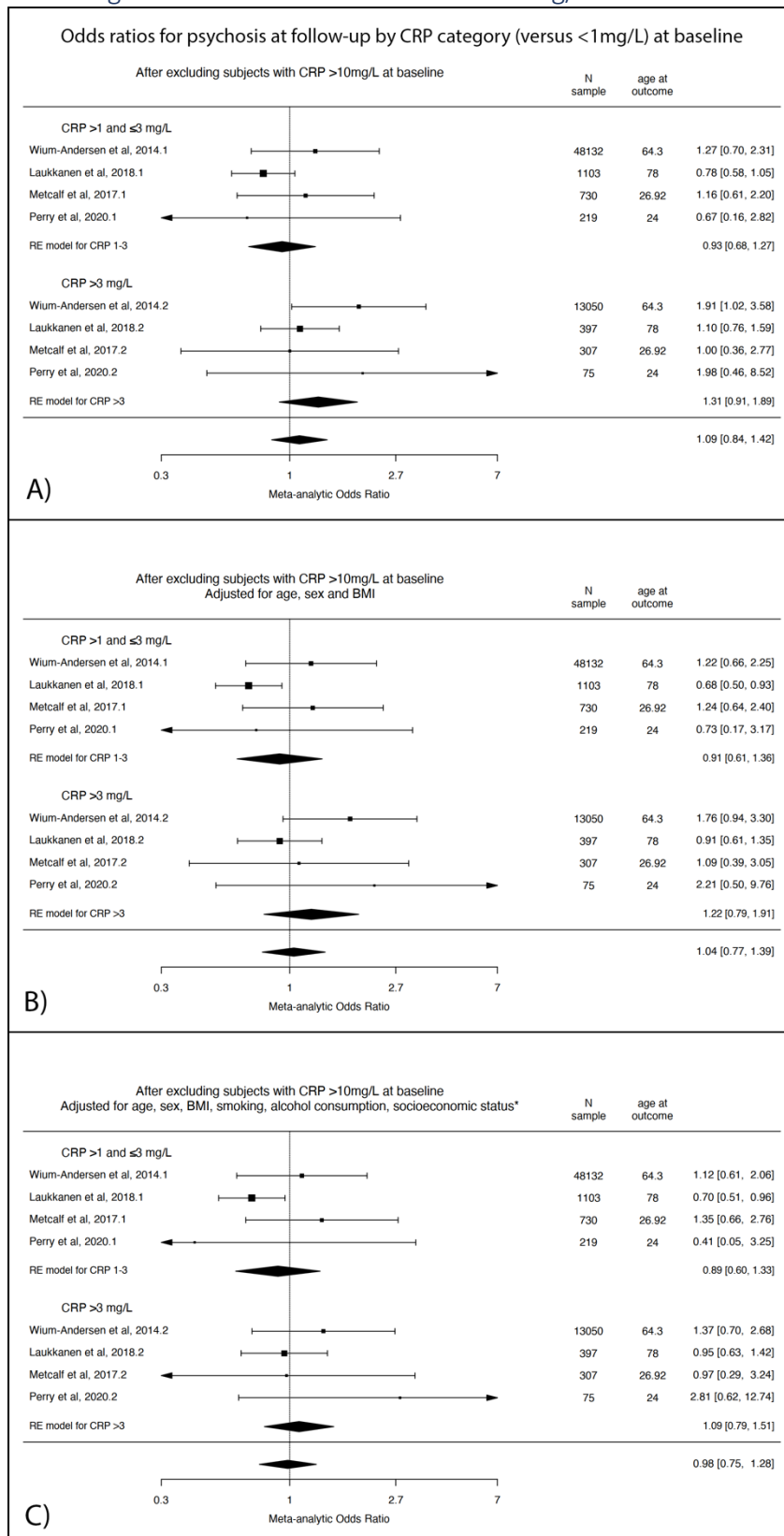

BMI, body mass index; CRP, C-reactive protein; mg/L, milligrams per litre

References:

Pillinger, T., Osimo, E.F., Brugger, S., Mondelli, V., McCutcheon, R.A., Howes, O.D., 2019. A Meta-analysis of Immune Parameters, Variability, and Assessment of Modal Distribution in Psychosis and Test of the Immune Subgroup Hypothesis. Schizophrenia Bulletin 45, 1120–1133.