Results from a Cochrane Systematic Review of the Science on AA/TSF

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SoAP Webinar May, 2020

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Acknowledgments

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Acknowledgments
Partial Funding

Key Points

DOES AA/TSF STILL HAVE RELEVANCE?

WHAT IS “COCHRANE SYSTEM”?

COCHRANE REVIEW AA/TSF PROCEDURES AND RESULTS

Is AA/TSF still relevant?

- Alcohol – global problem; especially in middle-high income countries
  - 3.3M deaths annually (10x > than all drugs)
  - Top risk factor for premature mortality among men of working age worldwide
  - 3rd Leading cause premature death U.S.
  - Genetically influenced; profound impact brain structure/ function; chronic, relapsing course…
  - Given this, absurd to refer people to church basements to work on a program of religiously-worded “steps”?
  - Surely, the only “steps” should be taking are those up and out of the church basement into the sunlight of real clinical science?

Addiction “Treatment” Facility

Addiction Treatment Facility

New York City Addiction Hospital Administrator 1937…

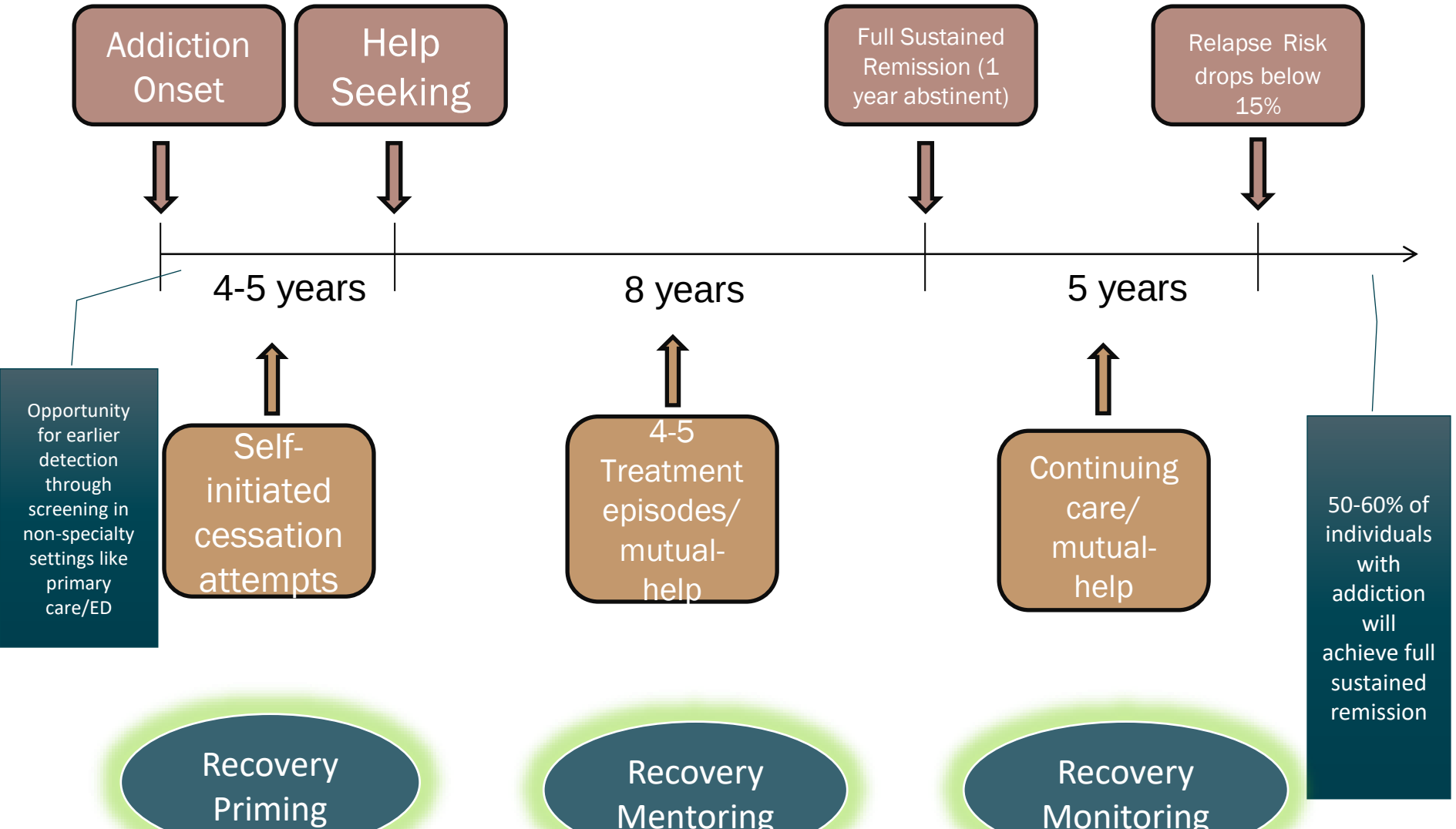
- “When my head doctor, Silkworth, began to tell me of the idea of helping drunks by spirituality, I thought it was crackpot stuff, but I’ve changed my mind. One day this bunch of ex-drunks of yours is going to fill Madison Square Garden”

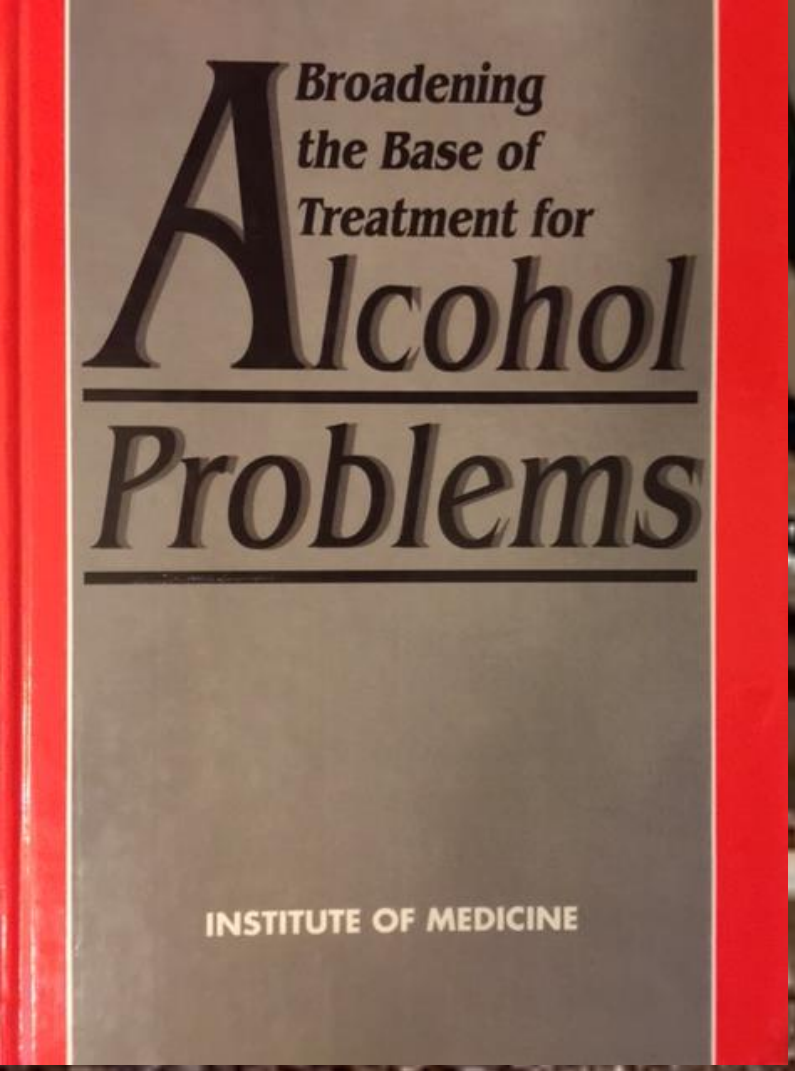
-AA, 1947

Clinical and Public Health Significance of AA Research

- Alcohol – global problem; especially in middle-high income countries
  - 3.3M deaths annually (10x > than all illicit drugs combined)
  - The top risk factor for premature mortality among men of working age worldwide
  - Major contributor to DALYs (particularly developed world)
- AA is a **freely available**, **ubiquitous**, **indigenous**, **flexible**, **recovery support** service operating in 65,000 groups each week, with approximately 1.5M members in the U.S.; a de facto part of system of care for AUD

The clinical course of addiction and achievement of stable recovery can take a long time …



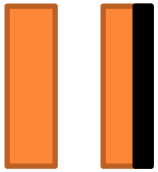

Broadening
the Base of
Treatment for
Alcohol
Problems
INSTITUTE OF MEDICINE


Research on
Alcoholics
Anonymous
OPPORTUNITIES AND ALTERNATIVES
Edited by
Barbara S. McCrady and
William R. Miller

TSF Delivery Modes

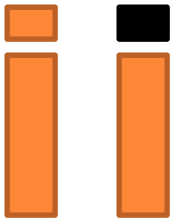
Stand alone
Independent therapy

Integrated into an existing therapy

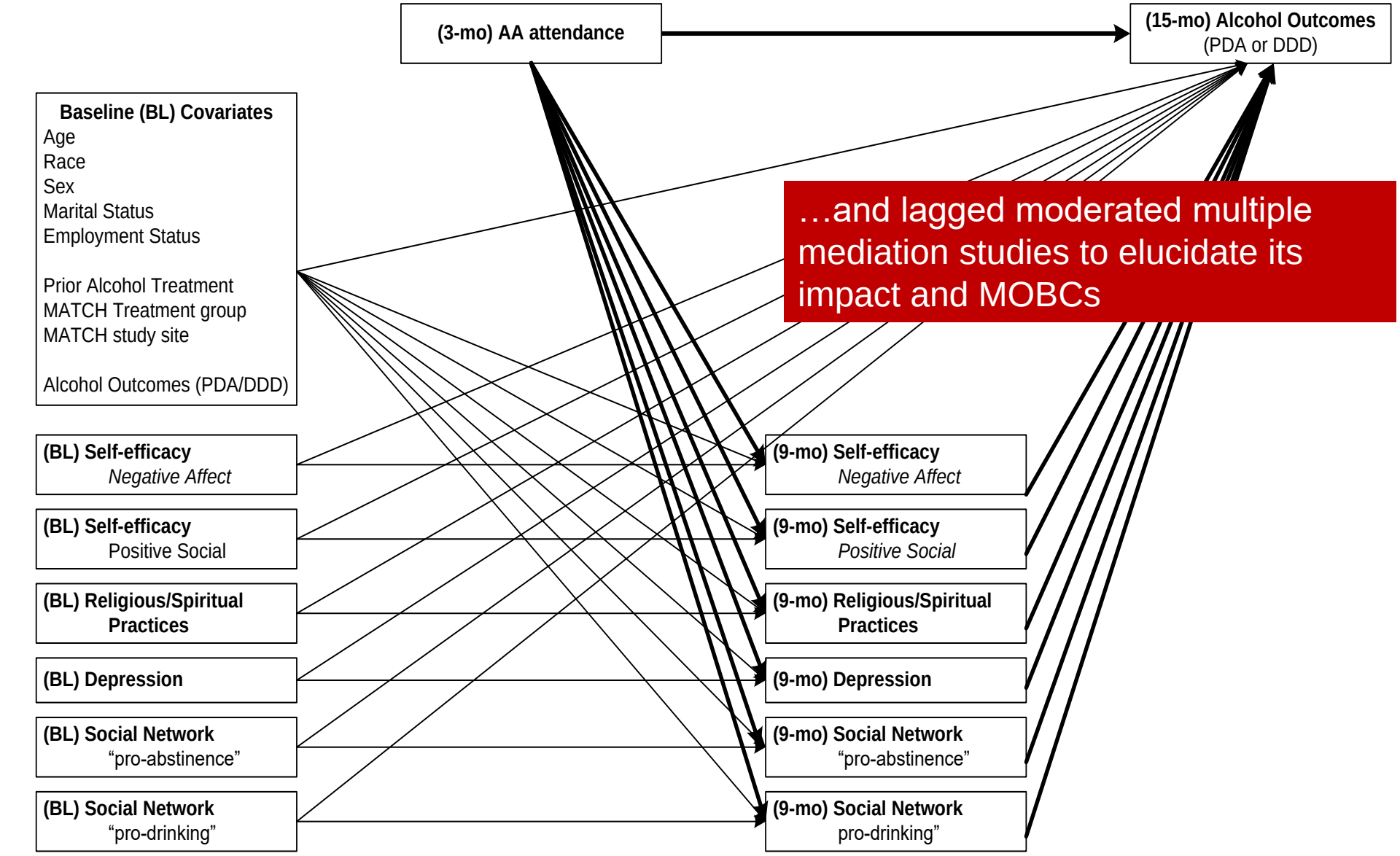


Component of a treatment package (e.g., an additional group)

As Modular appendage linkage component



In past 25 years, AA research has gone from contemporaneous correlational research to rigorous RCTs, quasi-experiments, cost utility, and MOBC research …


(3-mo) AA attendance
(15-mo) Alcohol Outcomes
(PDA or DDD)
Baseline (BL) Covariates
Age
Race
Sex
Marital Status
Employment Status
Prior Alcohol Treatment
MATCH Treatment group
MATCH study site
Alcohol Outcomes (PDA/DDD)
(BL) Self-efficacy
Negative Affect
(BL) Self-efficacy
Positive Social
(BL) Religious/Spiritual
Practices
(BL) Depression
(BL) Social Network
"pro-abstinence"
(BL) Social Network
"pro-drinking"
(9-mo) Self-efficacy
Negative Affect
(9-mo) Self-efficacy
Positive Social
(9-mo) Religious/Spiritual
Practices
(9-mo) Depression
(9-mo) Social Network
"pro-abstinence"
(9-mo) Social Network
pro-drinking"
…and lagged moderated multiple mediation studies to elucidate its impact and MOBCs

What is the Cochrane System?

The Cochrane Library (named after Archie Cochrane) is a collection of databases in medicine and other healthcare specialties provided by Cochrane and other organizations.

At its core is the collection of Cochrane Reviews, a database of systematic reviews and meta-analyses which summarize and interpret the results of medical research.

The Cochrane Library aims to make the results of well-conducted controlled trials readily available and is a key resource in evidence-based medicine.

One must apply first, have the topic and title approved, and then submit a protocol which is peer reviewed…

Cochrane Reviews Contain very specific procedures and format…

- Abstract and Plain Language Abstract
- Background and Rationale
- Comprehensive, systematic, searches
- Methods
  - Inclusion Criteria
  - Specified relevant Outcomes
  - Summary of Findings Tables
  - **Meta-analyses (use their own software for greater transparency)**
  - **Gradings of the quality of the evidence (GRADE system: directness, consistency, imprecision, publication bias)**
  - **Ratings of actual or potential biases (8 types)**
  - **Separate gradings of quality for economic studies (EVERS checklist)**
  - **Very rigorous methods editorial review**
  - **External Peer review**

  Discussion (includes formal subheadings including Implications for Practice and Research etc)

Cochrane Library

Cochrane Database of Systematic Reviews

Alcoholics Anonymous and other 12-step programs for alcohol use disorder (Review)

Kelly JF, Humphreys K, Ferri M

120 pages!

Kelly JF, Humphreys K, Ferri M.
Alcoholics Anonymous and other 12-step programs for alcohol use disorder.
Cochrane Database of Systematic Reviews 2020, Issue 3. Art. No.: CD012880.
DOI: 10.1002/14651858.CD012880.pub2.

www.cochranelibrary.com

WILEY

Cochrane Systematic Review on AA/TSF (2020)

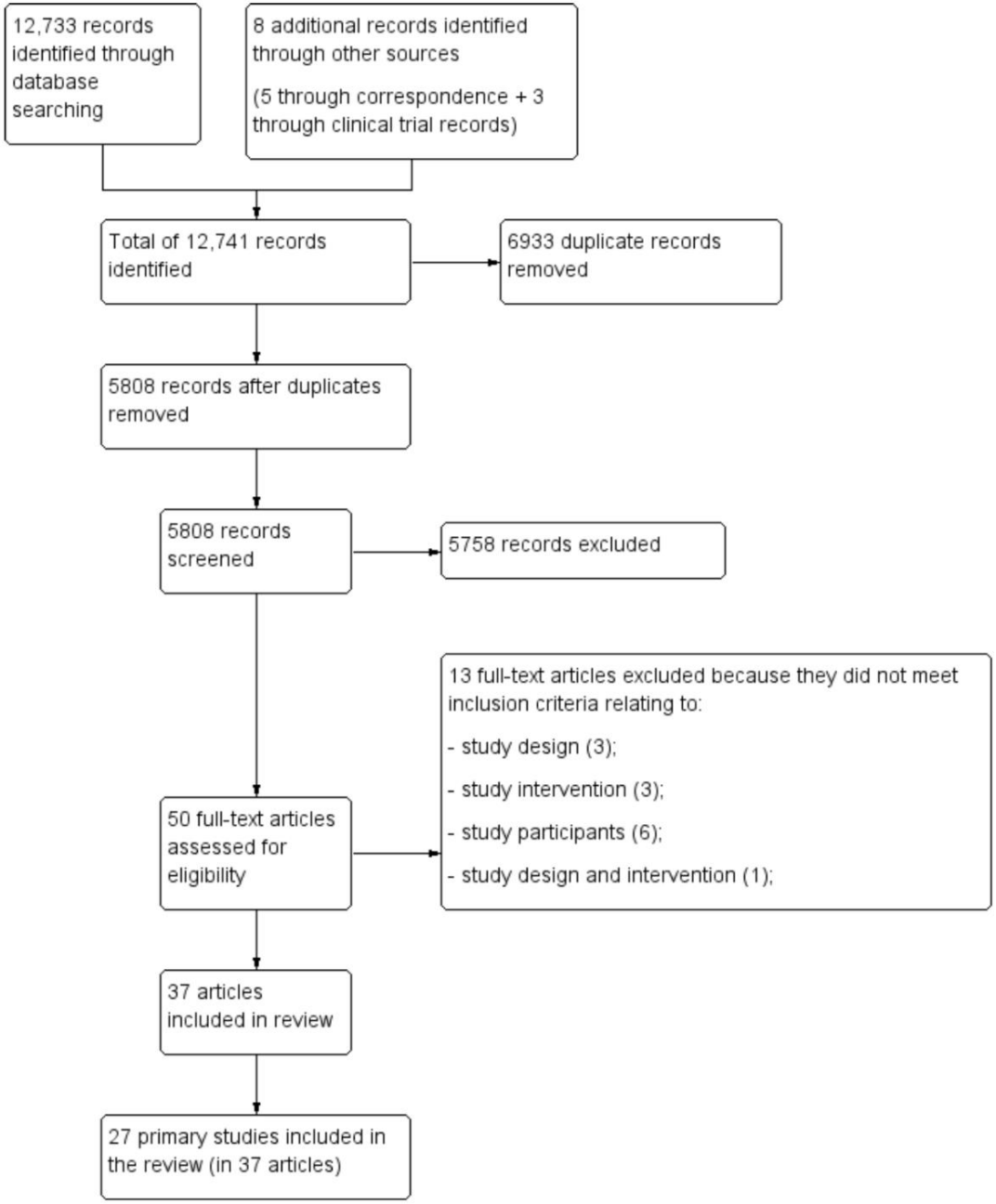
- Kelly, JF
- Humphreys, K
- Ferri, M

Selection Criteria

- We included randomized controlled trials (RCTs), quasi-RCTs, and non-randomized studies that compared AA/TSF with other interventions such as motivational enhancement therapy (MET) or cognitive-behavioral therapy (CBT), TSF treatment variants, or no treatment.
- Health care cost-offset (economic) studies were also included.
- Participants were non-coerced male and female adults with AUD.

CONSORT OF SEARCH

Figure 1. PRISMA study flow diagram.



Search Methods

Cochrane Drugs and Alcohol Group Specialized Register (via CRSLive), Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Embase, CINAHL and PsycINFO from inception to August 2019.

Also searched for ongoing and unpublished studies via ClinicalTrials.gov (www.clinicaltrials.gov) and WHO International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/).

All searches included non-English language literature. We hand searched references of topic-related systematic reviews and included studies.

Outcomes

Abstinence

- **Proportion of Patients Completely Abstinent:** 16 studies (n participants = 8,153)
- **Percent Days Abstinent (PDA):** 16 studies (n participants = 4,244)
- **Longest Period of Abstinence:** 2 studies (n participants = 148)

Drinking Intensity

- **Drinks per drinking day (DDD):** 8 studies (n participants = 2,650).
- **Percent Days Heavy Drinking (PDHD):** 3 studies (n participants = 648).

Alcohol-Related Consequences

- 8 studies (n participants = 3,281)

Alcohol Addiction Severity

- 7 studies (n participants = 1,616)

Economic Analyses

- 4 studies (n participants = 2,657)

Review Organization

- Studies organized along three dimensions:
  - Study Design
  - Degree of standardization/manualization
  - Type of Treatment comparison (e.g., different theoretical orientation vs AA/TSF variant)

Included studies by study design, degree of manualization, and theoretical orientation			
Study	**Design**	**Degree of manualization**	**Treatment comparison**
Blondell 2001	Non-randomized	Part/non-manualized	Different theoretical orientation
Blondell 2011	RCT	Part/non-manualized	Different theoretical orientation
Bogenschutz 2014	RCT	Part/non-manualized	Different theoretical orientation
Bowen 2014	RCT	Part/non-manualized	Different theoretical orientation
Brooks 2003	Quasi-RCT	Manualized	Different theoretical orientation
Brown 2002	RCT	Manualized	Different theoretical orientation
Davis 2002	RCT	Manualized	Different theoretical orientation
Grant 2017	Non-randomized	Part/non-manualized	TSF variant
Herman 2000	RCT	Part/non-manualized	Different theoretical orientation
Humphreys 1996	Non-randomized & Economic	Part/non-manualized	Different theoretical orientation
Kahler 2004	RCT	Manualized	TSF variant
Kaskutas 2009	Quasi-RCT	Part/non-manualized	TSF variant
Kelly 2017	RCT	Manualized	Different theoretical orientation
Litt 2007	RCT	Manualized	Different theoretical orientation
Litt 2016	RCT	Manualized	Different theoretical orientation
Lydecker 2010	Quasi-RCT	Manualized	Different theoretical orientation
Manning 2012	RCT	Part/non-manualized	TSF variant
MATCH 1997a	RCT	Manualized	Different theoretical orientation
McCrady 1996	RCT	Manualized	Different theoretical orientation
Mundt 2012	Economic	Part/non-manualized	TSF variant
Ouimette 1997	Non-randomized	Part/non-manualized	Different theoretical orientation & TSF variant
Timko 2006	RCT	Manualized	TSF variant
Timko 2011	Quasi-RCT	Manualized	TSF variant
Vederhus 2014	Quasi-RCT	Manualized	TSF variant
Walitzer 2009	RCT	Manualized	Different theoretical orientation & TSF variant
Walitzer 2015	RCT	Manualized	Different theoretical orientation
Zemore 2018	Non-randomized	Part/non-manualized	Different theoretical orientation

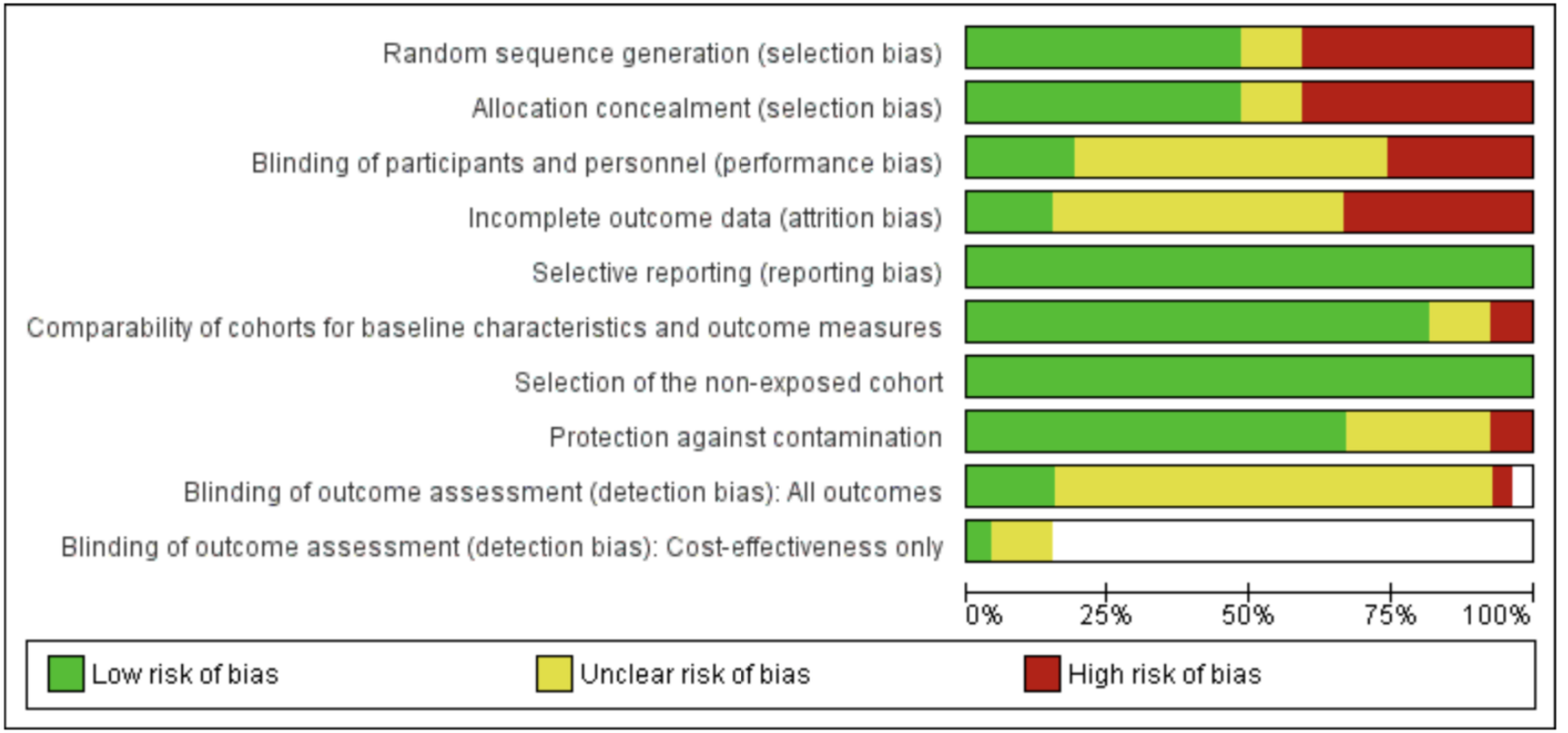
Included Studies (n participants)

- A total of 27 primary studies containing N=10,565 participants were included (21 RCTs/quasi-RCTs, 5 non-randomized, and 1 purely economic study) that reported follow-up results across 36 reports.

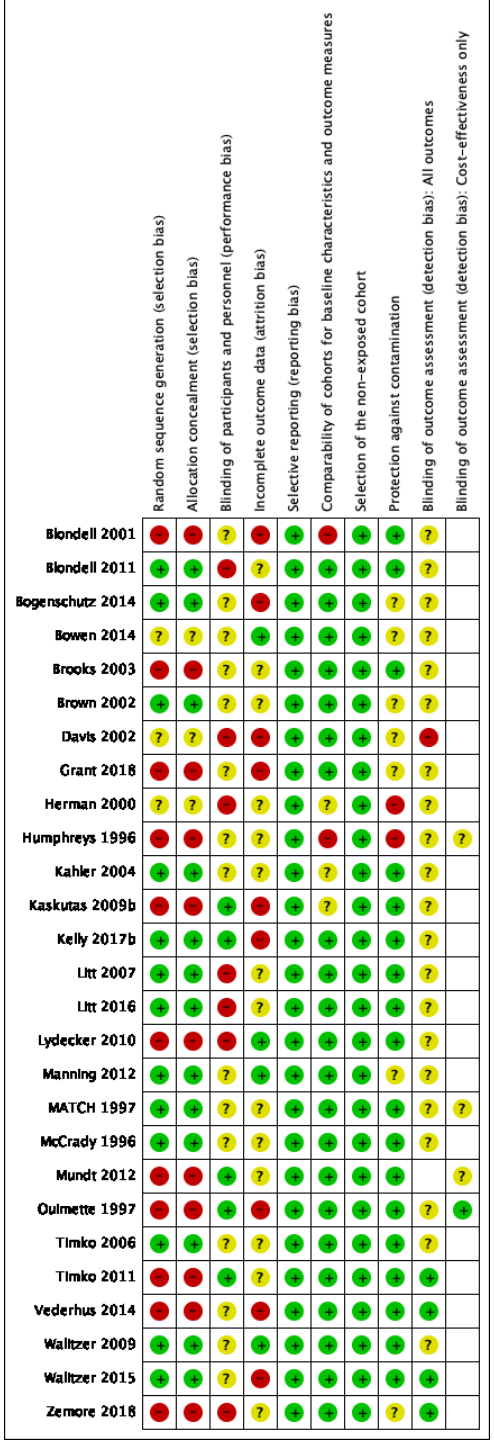
N of Studies/reports (n participants) by review dimension

Schematic overview of included studies												
Design	**RCT/Quasi-RCT** S = 21 R = 27 N = 5787				**Non-randomized** S = 5 R = 7 N = 4375				**Economic** S = 4 R = 5 N = 2657[a]			
Manualization	**All manualized** S = 15 R = 21 N = 4086		**Part/non-manualized** S = 6 R= 6 N = 1701		**All manualized** S = 0 R= 0 N= 0		**Part/non-manualized** S = 5 R = 7 N = 4375		**All manualized** S = 1 R = 1 N = 279		**Part/non-manualized** S = 3 R = 4 N = 2378	
Theoretical orientation	**Different** S = 11[b] R = 16 N = 3266	**Variant** S = 4 R = 5 N = 820	**Different** S = 4 R = 4 N = 1042	**Variant** S = 2 R = 2 N = 659	**Different** S = 0 R = 0 N = 0	**Variant** S = 0 R = 0 N = 0	**Different** S = 4[c] R = 6 N = 4180	**Variant** S = 1 R = 1 N = 195	**Different** S = 1 R = 1 N = 279	**Variant** S = 0 R = 0 N = 0	**Different** S = 2 R = 3 N = 1975	**Variant** S = 1 R = 1 N = 403
Analysis subgrouping	**1A**	**2A**	**1B**	**2B**	**3A**	**4A**	**3B**	**4B**	**5**	**5**	**5**	**5**

Risk of Bias Ratings



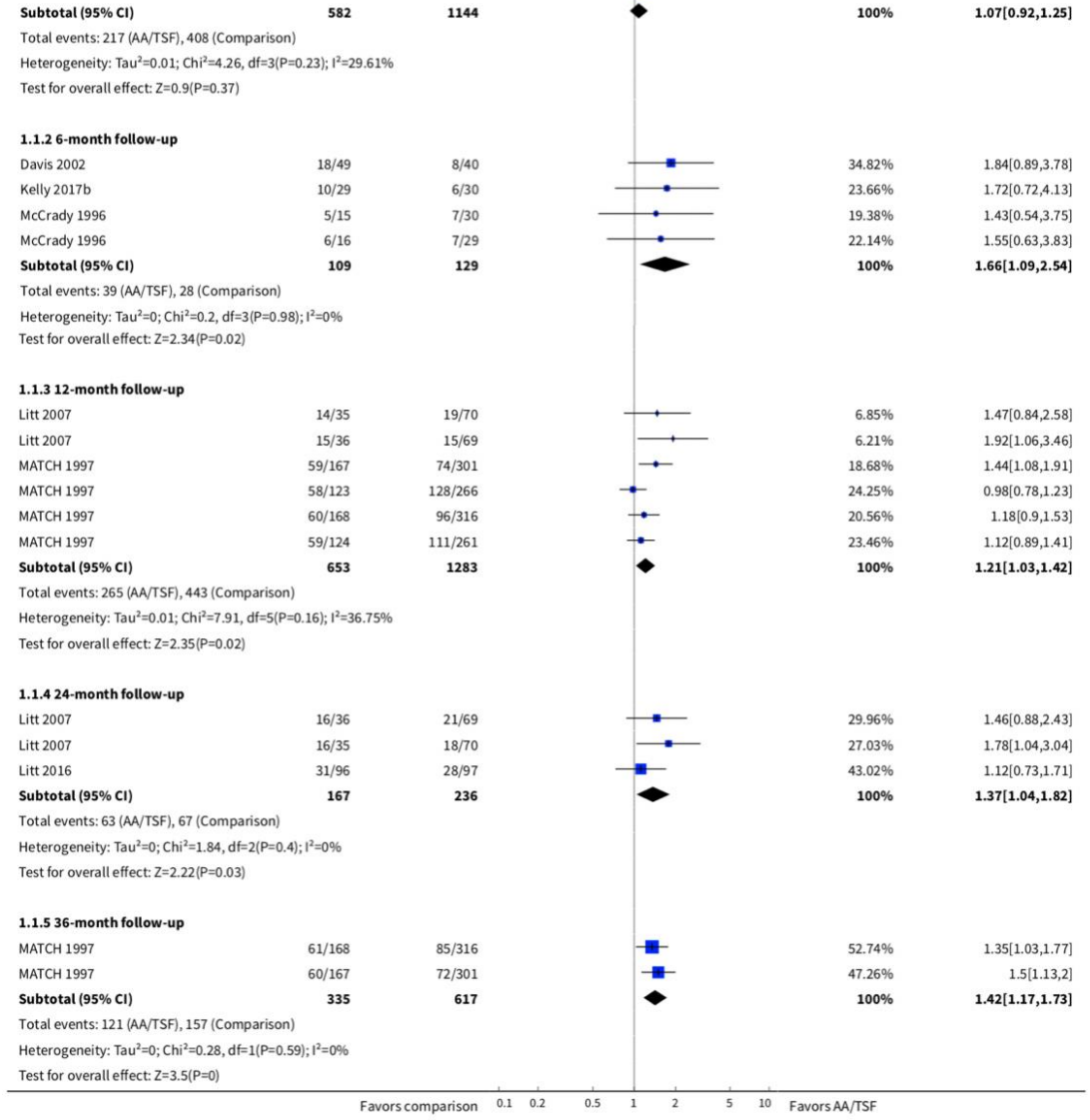
Risk of Bias Ratings Individual Studies



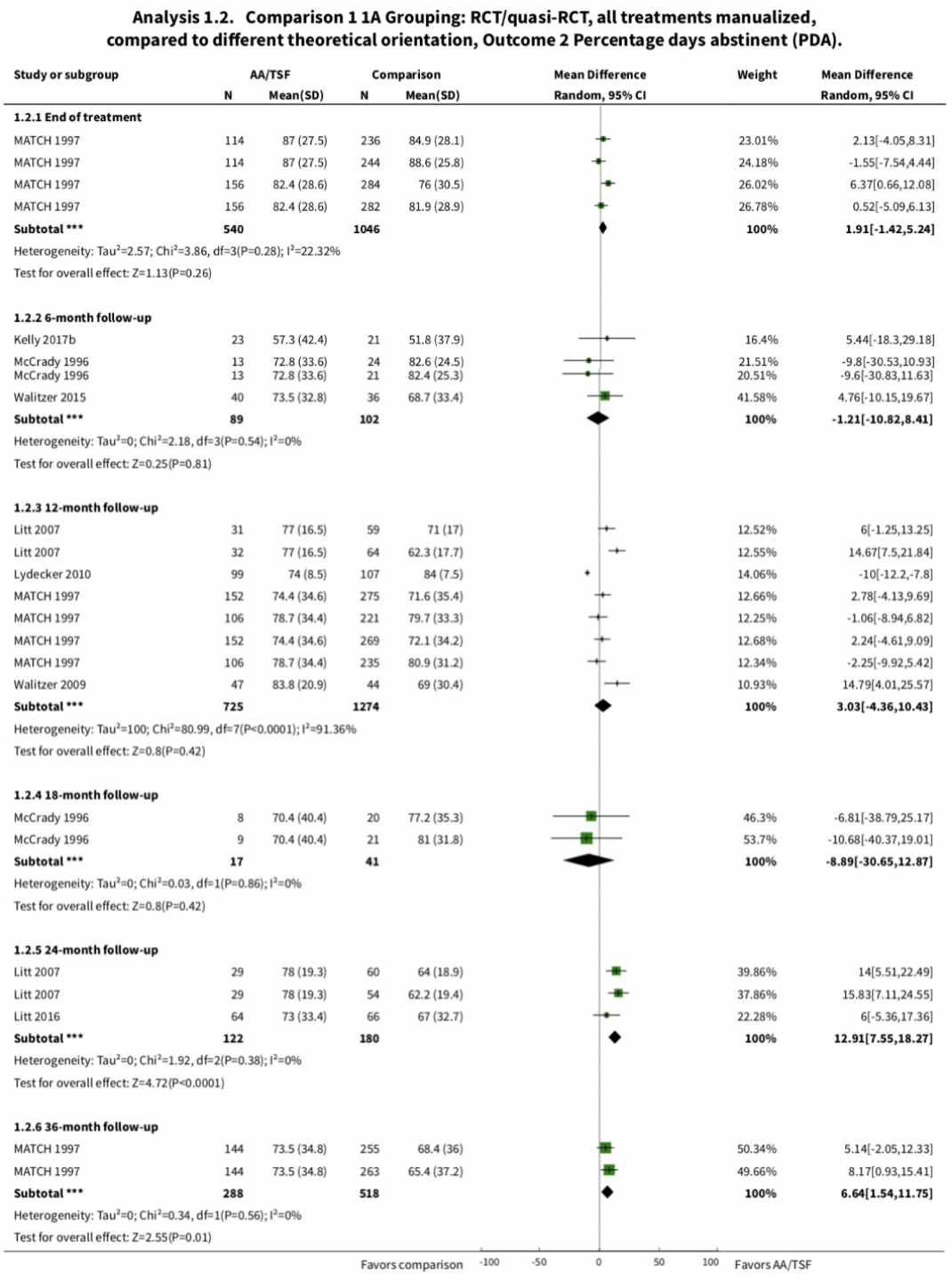
Forest plot of comparison: 1A GROUPING: RCTs, All Manualized, Compared to Different Theoretical Orientation, OUTCOME: 1.1 Proportion Completely Abstinent.

Analysis 1.1. Comparison 1 1A Grouping: RCT/quasi-RCT, all treatments manualized, compared to different theoretical orientation, Outcome 1 Proportion completely abstinent.

Study or subgroup	AA/TSF n/N	Comparison n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 End of treatment					
MATCH 1997	66/123	149/266		34.84%	0.96[0.79,1.17]
MATCH 1997	42/168	54/316		14.73%	1.46[1.02,2.09]
MATCH 1997	42/167	72/301		16.73%	1.05[0.76,1.46]
MATCH 1997	67/124	133/261		33.7%	1.06[0.87,1.3]
Subtotal (95% CI)	**582**	**1144**		**100%**	**1.07[0.92,1.25]**
Total events: 217 (AA/TSF), 408 (Comparison)					
Heterogeneity: Tau^2=0.01; Chi^2=4.26, df=3(P=0.23); I^2=29.61%					
Test for overall effect: Z=0.9(P=0.37)					
1.1.2 6-month follow-up					
Davis 2002	18/49	8/40		34.82%	1.84[0.89,3.78]
Kelly 2017b	10/29	6/30		23.66%	1.72[0.72,4.13]
McCrady 1996	5/15	7/30		19.38%	1.43[0.54,3.75]
McCrady 1996	6/16	7/29		22.14%	1.55[0.63,3.83]
Subtotal (95% CI)	**109**	**129**		**100%**	**1.66[1.09,2.54]**
Total events: 39 (AA/TSF), 28 (Comparison)					
Heterogeneity: Tau^2=0; Chi^2=0.2, df=3(P=0.98); I^2=0%					
Test for overall effect: Z=2.34(P=0.02)					
1.1.3 12-month follow-up					
Litt 2007	14/35	19/70		6.85%	1.47[0.84,2.58]
Litt 2007	15/36	15/69		6.21%	1.92[1.06,3.46]
MATCH 1997	59/167	74/301		18.68%	1.44[1.08,1.91]
MATCH 1997	58/123	128/266		24.25%	0.98[0.78,1.23]
MATCH 1997	60/168	96/316		20.56%	1.18[0.9,1.53]
MATCH 1997	59/124	111/261		23.46%	1.12[0.89,1.41]
Subtotal (95% CI)	**653**	**1283**		**100%**	**1.21[1.03,1.42]**
Total events: 265 (AA/TSF), 443 (Comparison)					
Heterogeneity: Tau^2=0.01; Chi^2=7.91, df=5(P=0.16); I^2=36.75%					
Test for overall effect: Z=2.35(P=0.02)					
1.1.4 24-month follow-up					
Litt 2007	16/36	21/69		29.96%	1.46[0.88,2.43]
Litt 2007	16/35	18/70		27.03%	1.78[1.04,3.04]
Litt 2016	31/96	28/97		43.02%	1.12[0.73,1.71]
Subtotal (95% CI)	**167**	**236**		**100%**	**1.37[1.04,1.82]**
Total events: 63 (AA/TSF), 67 (Comparison)					
Heterogeneity: Tau^2=0; Chi^2=1.84, df=2(P=0.4); I^2=0%					
Test for overall effect: Z=2.22(P=0.03)					
1.1.5 36-month follow-up					
MATCH 1997	61/168	85/316		52.74%	1.35[1.03,1.77]
MATCH 1997	60/167	72/301		47.26%	1.5[1.13,2]
Subtotal (95% CI)	**335**	**617**		**100%**	**1.42[1.17,1.73]**
Total events: 121 (AA/TSF), 157 (Comparison)					
Heterogeneity: Tau^2=0; Chi^2=0.28, df=1(P=0.59); I^2=0%					
Test for overall effect: Z=3.5(P=0)					

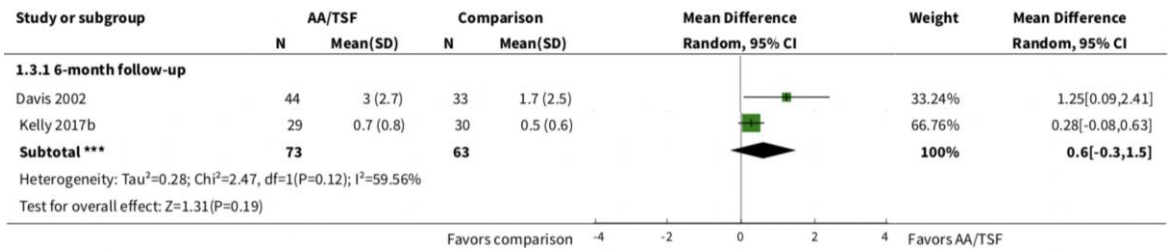


Forest plot of comparison: 1A GROUPING: RCTs, All Manualized, Compared to Different Theoretical Orientation, OUTCOME: 1.2 Percent Days Abstinent (PDA).

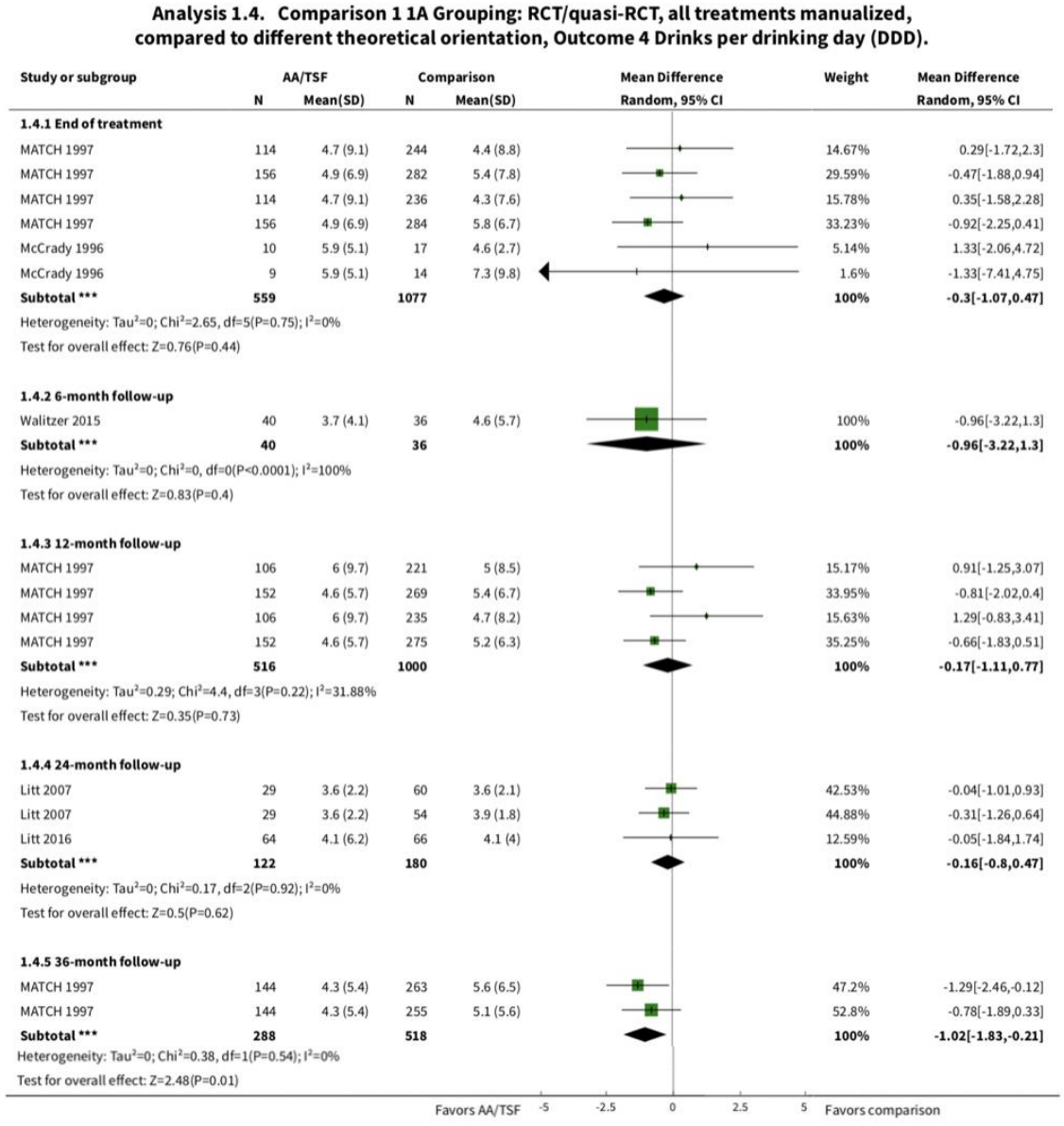


Forest plot of comparison: 1A GROUPING: RCTs, All Manualized, Compared to Different Theoretical Orientation, OUTCOME: 1.3 Longest Period of Abstinence (LPA).

Analysis 1.3. Comparison 1 1A Grouping: RCT/quasi-RCT, all treatments manualized, compared to different theoretical orientation, Outcome 3 Longest period of abstinence (LPA, months).

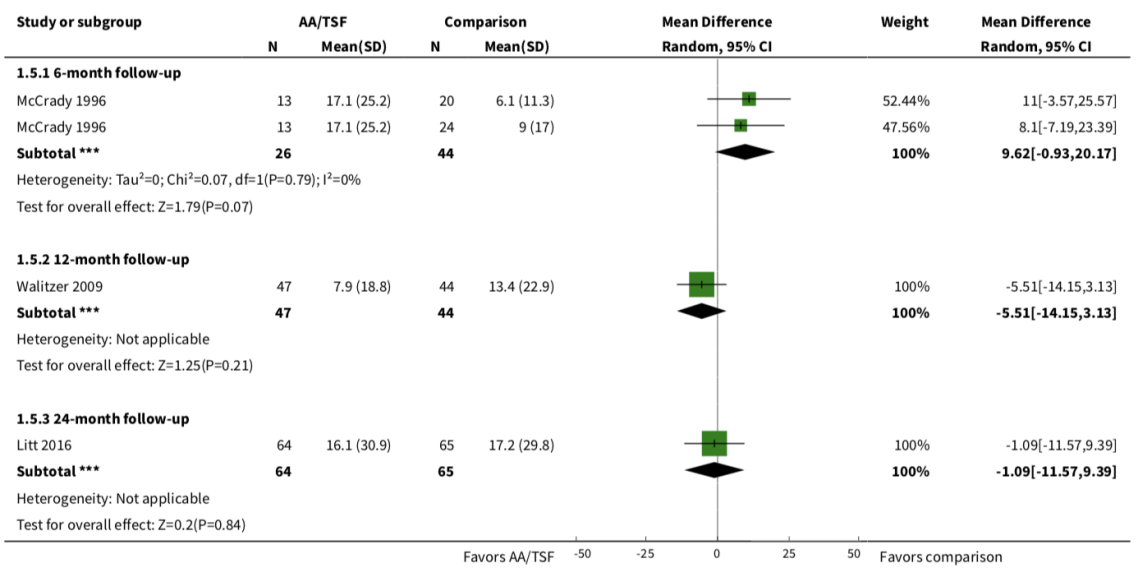


Forest plot of comparison: 1A GROUPING: RCTs, All Manualized, Compared to Different Theoretical Orientation, OUTCOME: 1.4 Drinks Per Drinking Day (DDD).



Forest plot of comparison: 1A GROUPING: RCTs, All Manualized, Compared to Different Theoretical Orientation, OUTCOME: 1.5 Percent Days Heavy Drinking (PDHD).

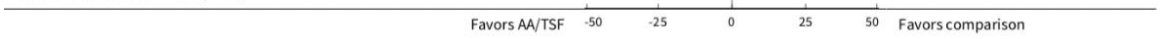
Analysis 1.5. Comparison 1 1A Grouping: RCT/quasi-RCT, all treatments manualized, compared to different theoretical orientation, Outcome 5 Percentage days heavy drinking (PDHD).



Forest plot of comparison: 1A GROUPING: RCTs, All Manualized, Compared to Different Theoretical Orientation, OUTCOME: 1.6 Alcohol-Related Consequences (DrInC).

Analysis 1.6. Comparison 1 1A Grouping: RCT/quasi-RCT, all treatments manualized, compared to different theoretical orientation, Outcome 6 Alcohol-related consequences (DrInC).

Study or subgroup	AA/TSF N	AA/TSF Mean(SD)	Comparison N	Comparison Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.6.1 End of treatment							
MATCH 1997	107	42.1 (52.1)	232	39.4 (51.6)		18.82%	2.68[-9.22,14.58]
MATCH 1997	153	58.3 (46.7)	289	68 (44)		32.06%	-9.76[-18.73,-0.79]
MATCH 1997	108	42.1 (52.1)	226	43.5 (51.4)		18.82%	-1.42[-13.32,10.48]
MATCH 1997	153	58.3 (46.7)	264	59.9 (45.9)		30.31%	-1.62[-10.87,7.63]
Subtotal ***	**521**		**1011**			**100%**	**-3.38[-8.66,1.9]**
Heterogeneity: Tau^2=1.66; Chi^2=3.18, df=3(P=0.36); I^2=5.63%							
Test for overall effect: Z=1.26(P=0.21)							
1.6.2 12-month follow-up							
Litt 2007	26	67.8 (25.6)	47	70.2 (19.5)		12.07%	-2.39[-13.69,8.9]
Litt 2007	27	67.8 (25.6)	51	72.9 (27.7)		10.23%	-5.1[-17.36,7.17]
MATCH 1997	110	49.5 (52.9)	235	45.5 (47.5)		11.43%	3.99[-7.62,15.59]
MATCH 1997	110	49.5 (52.9)	236	46.8 (53.5)		10.67%	2.73[-9.28,14.74]
MATCH 1997	148	48 (42.7)	267	52.8 (44.3)		20.34%	-4.81[-13.51,3.88]
MATCH 1997	148	48 (42.7)	274	55.2 (42)		21.34%	-7.13[-15.62,1.36]
Walitzer 2009	43	19.5 (25.3)	40	21.8 (23.6)		13.92%	-2.3[-12.81,8.22]
Subtotal ***	**612**		**1150**			**100%**	**-2.88[-6.81,1.04]**
Heterogeneity: Tau^2=0; Chi^2=3.48, df=6(P=0.75); I^2=0%							
Test for overall effect: Z=1.44(P=0.15)							
1.6.3 24-month follow-up							
Litt 2007	29	67.9 (25.6)	57	68.3 (24.2)		28.85%	-0.37[-11.58,10.85]
Litt 2007	28	67.9 (25.6)	51	66.2 (20.3)		30.11%	1.72[-9.26,12.7]
Litt 2016	64	64.9 (28.1)	66	71 (26.5)		41.04%	-6.1[-15.5,3.31]
Subtotal ***	**121**		**174**			**100%**	**-2.09[-8.11,3.93]**
Heterogeneity: Tau^2=0; Chi^2=1.25, df=2(P=0.54); I^2=0%							
Test for overall effect: Z=0.68(P=0.5)							



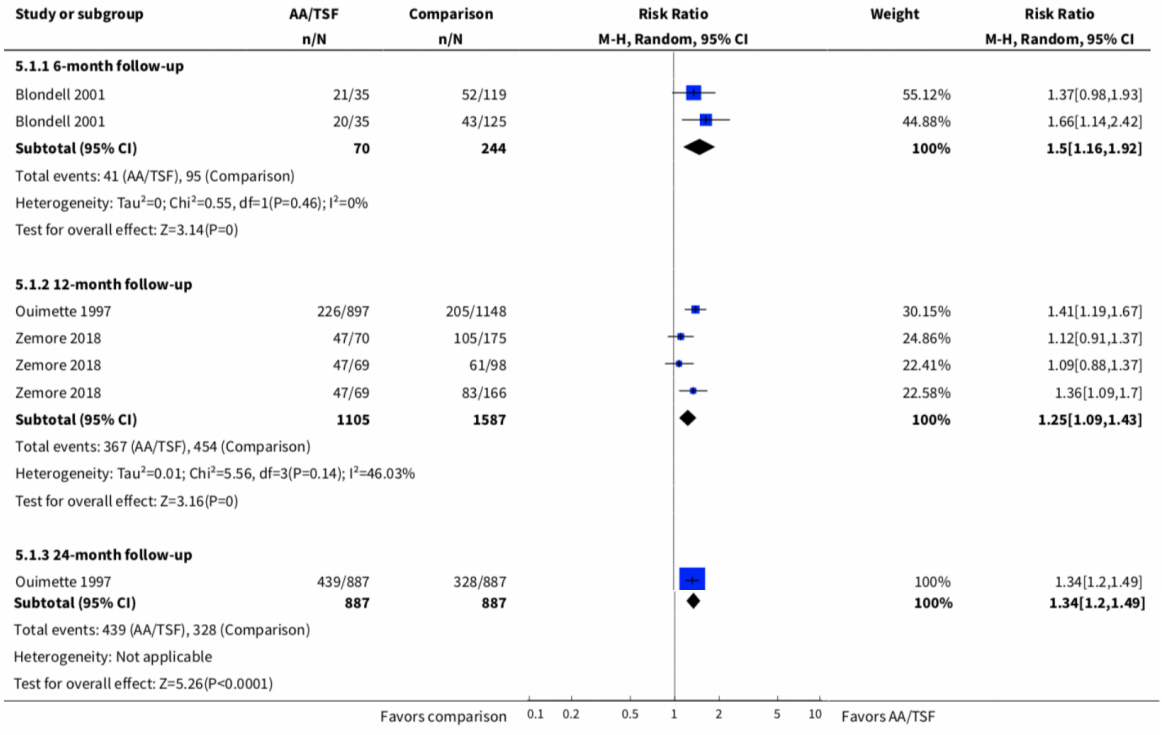
Forest plot of comparison: 2A GROUPING: RCTs, All Manualized, Compared to TSF Variant, OUTCOME: 3.1 Proportion of Patients Completely Abstinent.

Analysis 3.1. Comparison 3 2A Grouping: RCT/quasi-RCT, all treatments manualized, compared to TSF variant, Outcome 1 Proportion of participants completely abstinent.

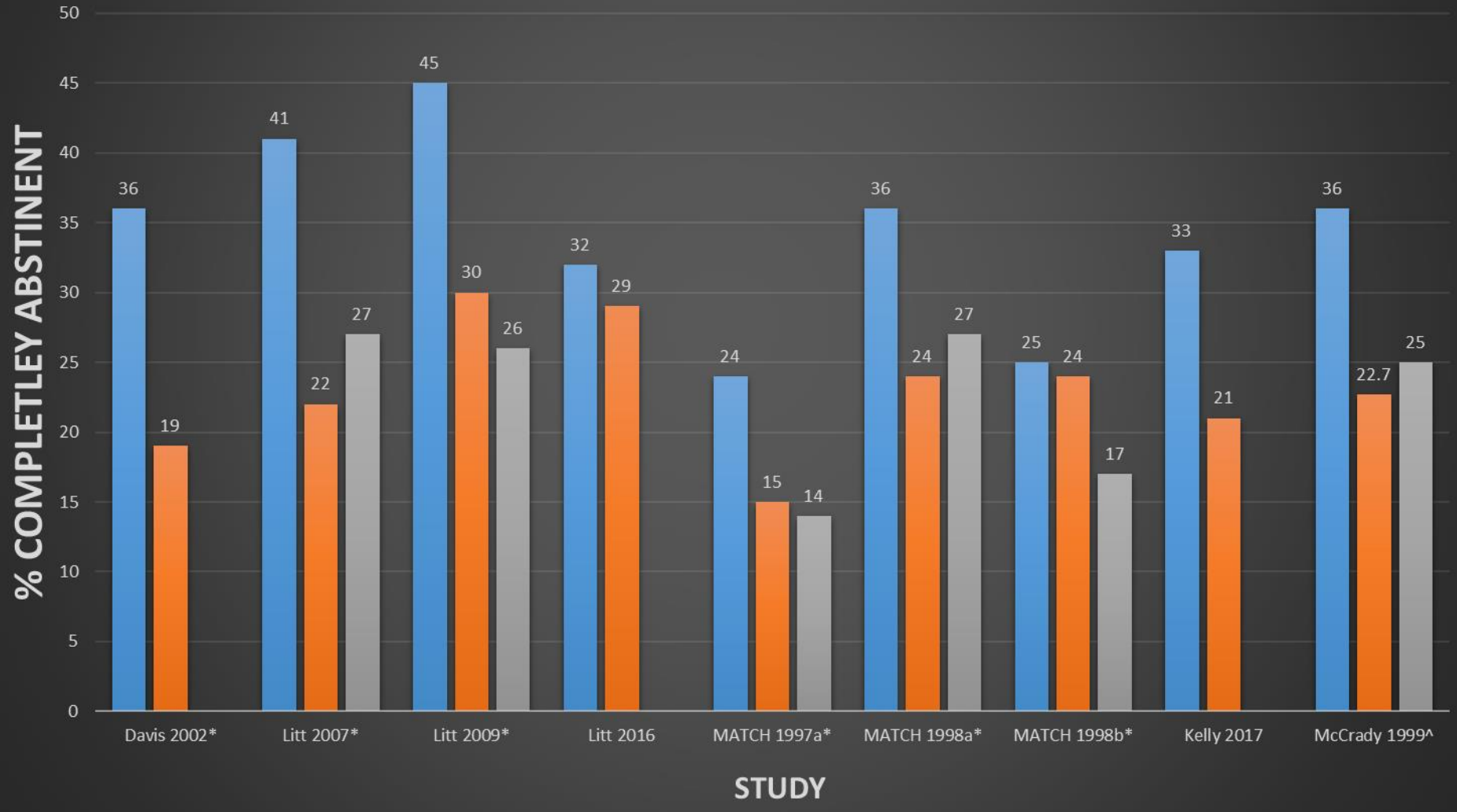
Study or subgroup	AA/TSF n/N	Comparison n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 6-month follow-up					
Timko 2006	138/181	115/164		64.07%	1.09[0.96,1.24]
Timko 2011	85/142	83/145		28.03%	1.05[0.86,1.27]
Vederhus 2014	30/68	33/72		7.9%	0.96[0.67,1.39]
Subtotal (95% CI)	**391**	**381**		**100%**	**1.07[0.96,1.18]**
Total events: 253 (AA/TSF), 231 (Comparison)					
Heterogeneity: $Tau^2=0$; $Chi^2=0.45$, df=2(P=0.8); $I^2=0\%$					
Test for overall effect: Z=1.2(P=0.23)					
3.1.2 12-month follow-up					
Timko 2006	83/161	59/146		100%	1.28[1,1.63]
Subtotal (95% CI)	**161**	**146**		**100%**	**1.28[1,1.63]**
Total events: 83 (AA/TSF), 59 (Comparison)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.93(P=0.05)					

Forest plot of comparison: 3B: Non-Randomized, 1+ Conditions Non-Manualized, Compared to Different Theoretical Orientation, OUTCOME: 5.1 Proportion of Patients Completely Abstinent.

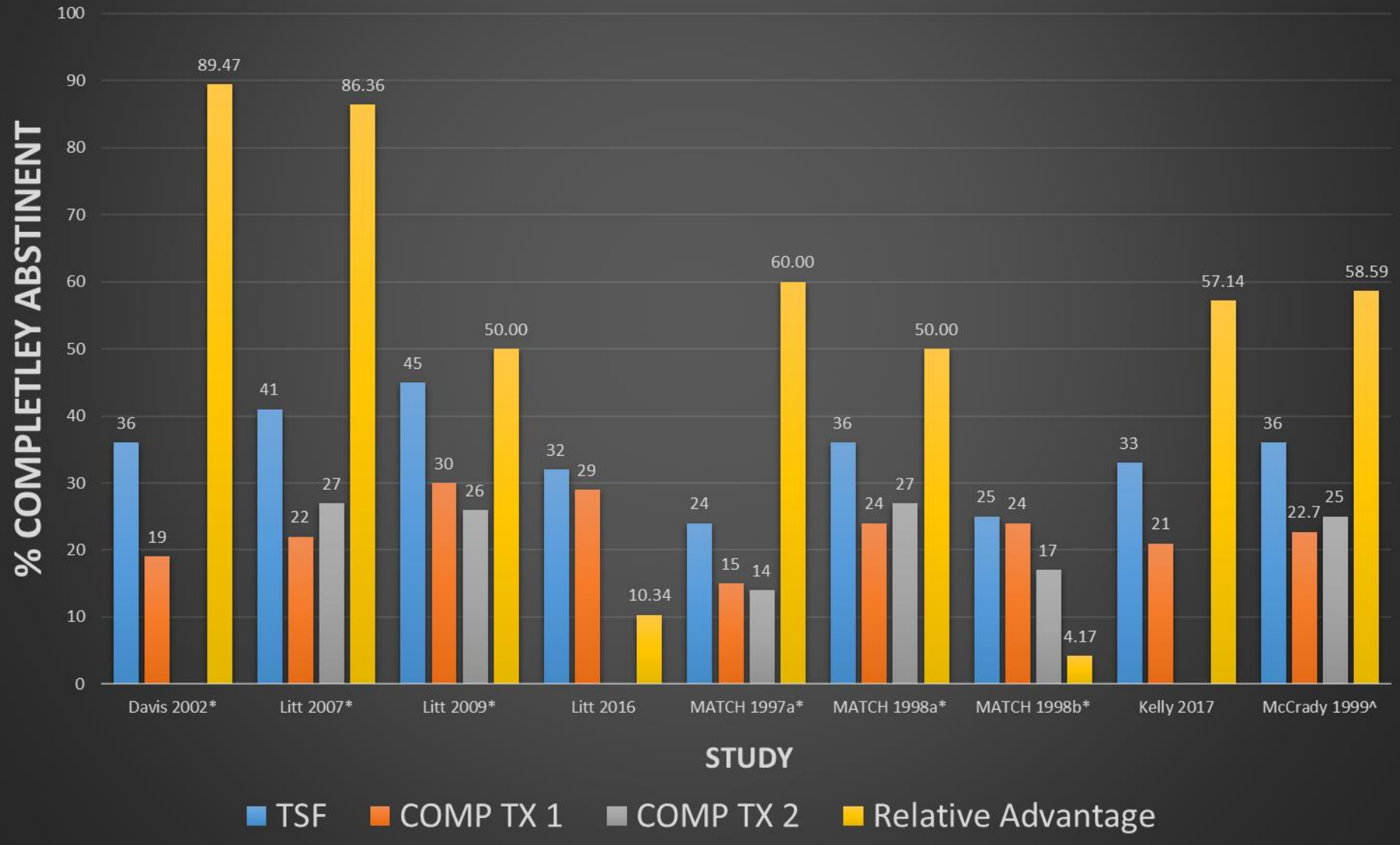
Analysis 5.1. Comparison 5 3B: Non-randomized, 1+ treatments non-manualized, compared to different theoretical orientation, Outcome 1 Proportion of participants completely abstinent.



TSF Compared to Different Theoretical Orientation Treatments (RCTs all Manualized)



TSF Compared to Different Theoretical Orientation Treatments (RCTs all Manualized)



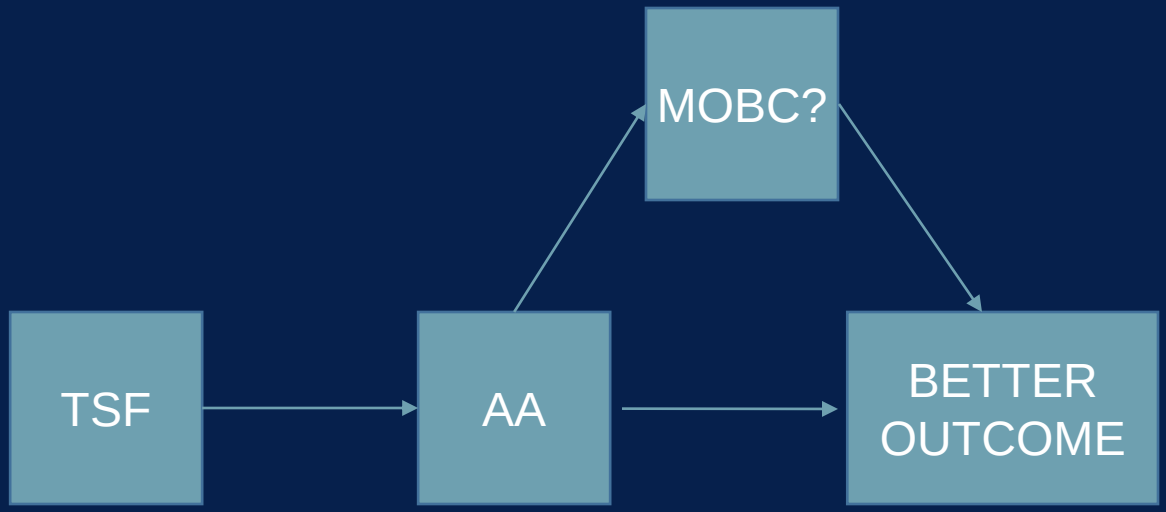
Economic Studies

Healthcare Cost Savings

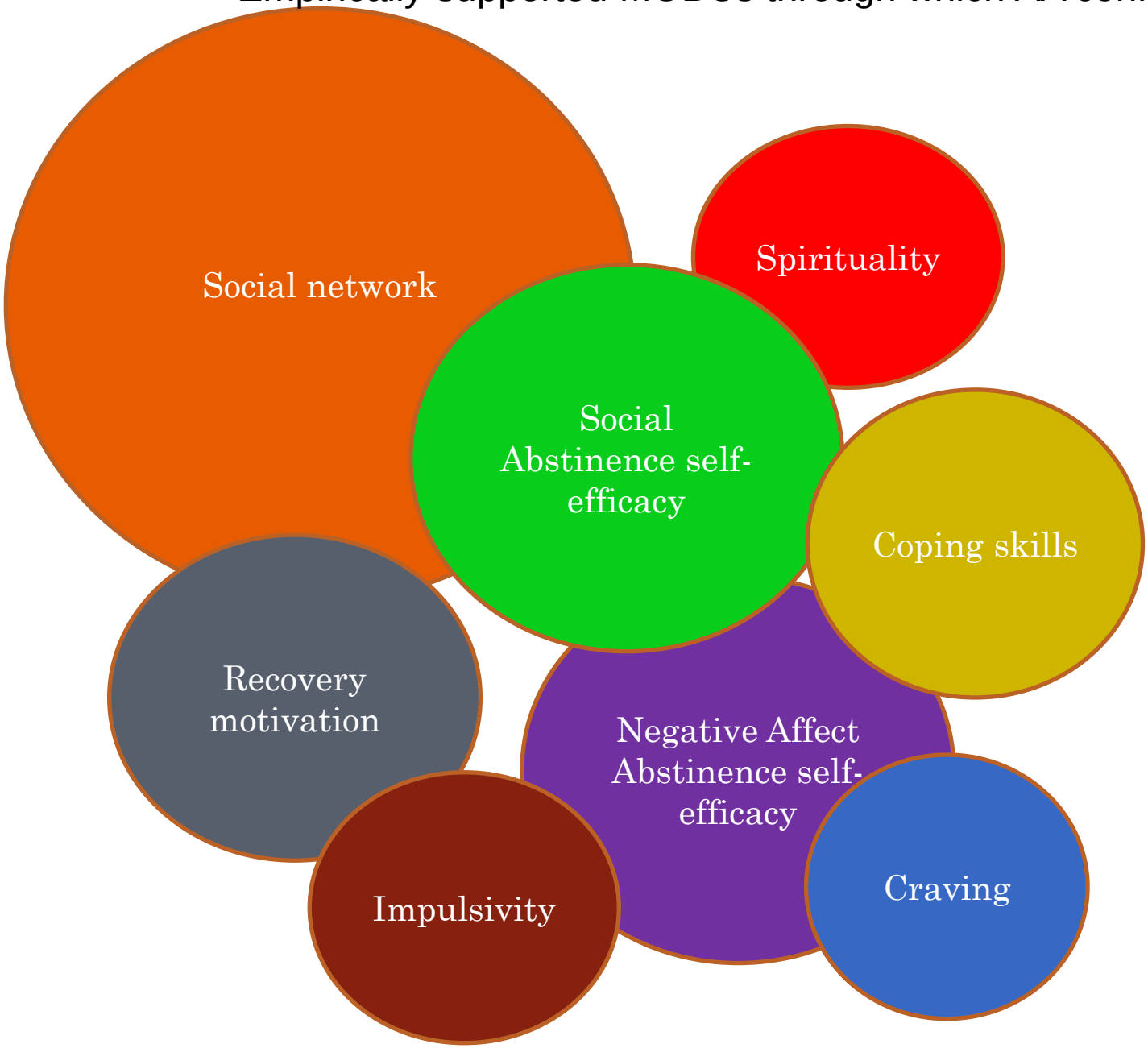
- 3/4 included studies in this category (n reports = 4/5; found sig. health care cost saving in favor of the AA/TSF condition.
- Economic analyses found benefits in favor of AA/TSF relative to outpatient treatment, and CBT interventions.
- Magnitude quite large. In addition to sig. increased abstinence, compared to CBT interventions delivered in residential VA, AA/TSF reduces mental health and substance use related healthcare costs over the next two years by over $10,000 per patient (converted to 2018 U.S. dollars).
- More than 1M people treated for AUD in U.S. annually - reducing their health care costs by this amount would produce an large aggregate economic saving (e.g., >$10 billion in the U.S. alone) as well as improving clinical outcomes.

In Studies the conducted and reported mediational analyses…AA/TSF Causal chain supported…

What about support for causal chain of purported mobc of AA on outcomes?



Empirically-supported MOBCs through which AA confers benefit



AA/TSF Findings Summary

For alcohol-related outcomes other than complete abstinence, AA and professionally-delivered TSF interventions are at least as effective as other well-established treatments.

For abstinence outcomes, AA and TSF interventions are as effective or better than other well-established treatments.

Implementing AA and TSF also appear to produce substantial health care cost savings.

Mediational analyses demonstrate clinically delivered TSF produces its benefits largely through its ability to foster increased AA participation during and, importantly, following the end of formal treatment.