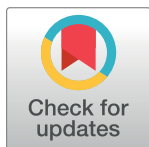RESEARCH ARTICLE

Effectiveness and treatment moderators of internet interventions for adult problem drinking: An individual patient data meta-analysis of 19 randomised controlled trials

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Abbreviations: AUDIT, The Alcohol Use Disorders Identification Test; AUDIT-C, The Alcohol Use Disorders Identification Test (brief, 3 items); BAI, brief alcohol intervention; BSC, behavioural self-control; CBT, cognitive-behavioural therapy; FAST, Fast Alcohol Screening Test; GP, general practitioner; iAI, internet-based alcohol intervention; IPD, individual patient data; IPDMA, individual patient data meta-analysis; ITT, intention-to-treat; LMM, linear mixed model; MAR, missing at random; MCAR, missing completely at random; MI, motivational interviewing; MNAR, missing-not-at-random; NNT, number needed to treat; OR, odds ratio; PNF, personalised normative feedback; RCT, randomised controlled trial; SU, standard unit of alcohol consumption based on 10 grams of ethanol; TLFB, time line follow-back; TR, treatment response; WLC, waitlist-controlled.

Abstract

Background

Face-to-face brief interventions for problem drinking are effective, but they have found limited implementation in routine care and the community. Internet-based interventions could overcome this treatment gap. We investigated effectiveness and moderators of treatment outcomes in internet-based interventions for adult problem drinking (iAIs).

Methods and findings

Systematic searches were performed in medical and psychological databases to 31 December 2016. A one-stage individual patient data meta-analysis (IPDMA) was conducted with a linear mixed model complete-case approach, using baseline and first follow-up data. The primary outcome measure was mean weekly alcohol consumption in standard units (SUs, 10 grams of ethanol). Secondary outcome was treatment response (TR), defined as less than 14/21 SUs for women/men weekly. Putative participant, intervention, and study moderators were included. Robustness was verified in three sensitivity analyses: a two-stage IPDMA, a one-stage IPDMA using multiple imputation, and a missing-not-at-random (MNAR) analysis. We obtained baseline data for 14,198 adult participants (19 randomised controlled trials [RCTs], mean age 40.7 [SD = 13.2], 47.6% women). Their baseline mean weekly alcohol consumption was 38.1 SUs (SD = 26.9). Most were regular problem drinkers (80.1%, SUs 44.7, SD = 26.4) and 19.9% (SUs 11.9, SD = 4.1) were binge-only drinkers. About one third were heavy drinkers, meaning that women/men consumed, respectively, more than 35/50 SUs of alcohol at baseline (34.2%, SUs 65.9, SD = 27.1). Post-intervention data were available for 8,095 participants. Compared with controls, iAI participants showed a greater mean weekly decrease at follow-up of 5.02 SUs (95% CI −7.57 to −2.48, p < 0.001) and a higher rate of TR (odds ratio [OR] 2.20, 95% CI 1.63–2.95, p < 0.001, number needed to treat [NNT] = 4.15, 95% CI 3.06–6.62). Persons above age 55 showed higher TR than their younger counterparts (OR = 1.66, 95% CI 1.21–2.27, p = 0.002). Drinking profiles were not significantly associated with treatment outcomes. Human-supported interventions were superior to fully automated ones on both outcome measures (comparative reduction: −6.78 SUs, 95% CI −12.11 to −1.45, p = 0.013; TR: OR = 2.23, 95% CI 1.22–4.08, p = 0.009). Participants treated in iAIs based on personalised normative feedback (PNF) alone were significantly less likely to sustain low-risk drinking at follow-up than those in iAIs based on integrated therapeutic principles (OR = 0.52, 95% CI 0.29–0.93, p = 0.029). The use of waitlist control in RCTs was associated with significantly better treatment outcomes than the use of other types of control (comparative reduction: −9.27 SUs, 95% CI −13.97 to −4.57, p < 0.001; TR: OR = 3.74, 95% CI 2.13–6.53, p < 0.001). The overall quality of the RCTs was high; a major limitation included high study dropout (43%). Sensitivity analyses confirmed the robustness of our primary analyses.

Conclusion

To our knowledge, this is the first IPDMA on internet-based interventions that has shown them to be effective in curbing various patterns of adult problem drinking in both community and healthcare settings. Waitlist control may be conducive to inflation of treatment outcomes.

Author summary

Why was this study done?

- Global estimations continue to show increasing morbidity, mortality, and social harm caused by all types of problem drinking.

- Face-to-face brief interventions for problem drinking are effective but rarely used.

- Internet-based interventions could overcome this treatment gap.

- We investigated effectiveness and moderators of treatment outcomes in internet-based interventions for adult problem drinking.

What did the researchers do and find?

- We conducted a one-stage individual patient data meta-analysis (IPDMA). This is, to our knowledge, the first study to identify moderators at the participant, intervention, and study design levels that are associated with treatment outcomes in internet-based interventions for adult problem drinking.

- Our IPDMA included 14,198 adults at baseline from 19 randomised controlled trials who exhibited various profiles of problem drinking. We obtained posttreatment data for 8,095 participants.

- Our results show that internet-based alcohol interventions in both community and healthcare populations are effective in reducing mean weekly alcohol consumption and in achieving adherence to low-risk drinking limits.

- We did not find differences in impact related to drinking profiles, meaning that people exceeding risk limits to a smaller or a larger degree benefited from the interventions, as did binge-only drinkers. Human-guided interventions showed a stronger impact on treatment outcome than fully automated ones, but waitlist design controls may inflate outcomes.

What do these findings mean?

- The health gains of internet-based alcohol interventions could be substantial, because such programmes can reach high numbers of problem drinkers by virtue of their swift entry procedures and their easy scalability.

- Future research should seek to identify categories of people for whom such interventions work best, to analyse how the interventions work and to determine what delivery contexts are most favourable. It should explore which patient populations could benefit most from referral to unguided forms and which would be more amenable to guidance by GPs or other professionals.

Introduction

Global estimations continue to show increasing physical and psychological morbidity, all-cause and specific-cause mortality, and social harm deriving from all types of alcohol misuse. Usually, a positive and linear association is seen between increased consumption and related health risks [1]. A number of factors underlie this mounting health burden. These include increases in the prevalence of alcohol consumers due to population growth and societal ageing, an absolute increase in adult alcohol consumption due to greater wealth and wider acceptance of alcohol use, and escalating alcohol use amongst women and the elderly. At the same time, there are growing insights into health risks connected with even minimal levels of alcohol consumption [2,3].

Brief alcohol interventions (BAIs) in primary care and community settings have been found clinically and cost-effective, with effect sizes in the small to moderate range, for reducing both hazardous drinking (which increases the risk of physical or psychological harm) and harmful drinking (which has already caused some damage) [4]. Together, their target groups are referred to as 'problem drinkers' to distinguish them from drinkers with alcohol use disorders, for whom more intensive treatments are recommended [5]. Problem drinkers account for the highest prevalence of alcohol misuse. Based on accumulated evidence, many national and professional guidelines now recommend brief interventions for problem drinkers in primary care settings and among community populations [6]. These interventions are comprised mostly of brief single or multiple sessions (up to six) and are based on personalised normative feedback (PNF) [7] or combinations of PNF, motivational interviewing (MI) [8], cognitive-behavioural therapy (CBT) [9], or behavioural self-control (BSC) principles [10]. Despite the ample evidence available, the actual impact of BAIs on curbing the prevalence of problem drinking in the wider population has been disappointingly low. The main factors in the weak impact include problems with implementation, as relatively few healthcare professionals actually administer BAIs; in addition, only a small proportion of patients who might benefit are actually offered BAIs, and even fewer accept the offer [11].

Internet-based alcohol interventions (iAIs) may overcome some of these problems by virtue of their low-threshold accessibility, their high scalability, and their acceptability to problem drinkers, as was recently echoed by McCambridge and Saitz [11]. Major advantages of iAIs, as perceived by many problem drinkers, are reduced stigma and greater comfort about disclosing drinking problems. The majority of iAIs are based on manualised therapeutic principles similar to those in BAIs. They are offered in unguided and guided formats. Unguided iAIs are fully automated interventions that participants can perform without human guidance. Guided interventions provide human support to guide participants through the intervention, mainly via asynchronous secure email contact [12]. The support may come from health professionals or trained volunteers. Meta-analytic studies have shown that unguided iAIs, in particular, are now used on a wider scale than conventional BAIs [13]. They have been found clinically effective (small effects) in reducing mean weekly adult alcohol consumption as compared with controls [14]. As a result, iAIs have been incorporated into some clinical guidelines for treating problem drinking in primary care [15].

All this notwithstanding, various uncertainties still surround the evidence base for iAIs. First of all, still little is known about whether women and older people derive benefits comparable to those seen for male and younger problem drinkers. Such knowledge is important in view of the rising prevalence rates of problem drinking among women and the elderly and their underrepresentation in many intervention studies [16]. Secondly, problem drinking actually embraces several different drinking profiles, and only a few iAI studies have investigated whether these might moderate treatment outcomes [17]. Such profiles include exceeding the

advised weekly alcohol limits to a moderate ('regular drinking') or a serious degree ('heavy drinking') and 'binge-only drinking', whereby alcohol users episodically exceed the maximum advised intakes per drinking occasion. Such divergent drinking profiles may or may not necessitate different interventions. Thirdly, there is the question of whether guided iAIs are more effective than unguided ones—a finding reported for CBT-based internet interventions for common mental disorders such as depression [18]. A related question is whether iAI treatment outcomes might vary according to the therapeutic orientation of the intervention.

The few moderator analyses conducted to date had a common limitation: they were statistically underpowered to properly address such questions [14]. To overcome this major problem, we conducted an individual patient data meta-analysis (IPDMA) that boosted the number of participants studied and thereby the statistical power. That enabled us to better evaluate the overall effectiveness of iAIs in reducing alcohol consumption, as well as to explore statistically significant differences within the data by performing moderator analyses on treatment outcomes, with a focus on participant, intervention, and study design characteristics.

Materials and methods

Identification and selection of randomised controlled trials

PsycINFO, Science Citation Index Expanded, Social Sciences Citation Index, Arts and Humanities Citation Index, CINAHL, PubMed, and EMBASE were searched up to 31 December 2016. All papers retrieved were evaluated by independent assessors (HR, EK, or NBo) (for search string, see S1 Data).

Eligibility criteria

Randomised controlled trials (RCTs) were eligible if they (1) studied people aged ≥18 with quantifiable levels of alcohol consumption that exceeded recommendations for low-risk drinking; (2) compared an iAI with a control condition (e.g., assessment only, waitlist, or minimal intervention); (3) studied an iAI based on therapeutic principles such as PNF, BSC, CBT, MI, or combinations thereof; and (4) studied either an unguided or a guided intervention or both. RCTs in populations of students or pregnant women were excluded. Primary authors of identified trials were asked to provide their raw RCT data for a set of pre-identified variables (HR/EK, S2 Data and see S4 Data for data access contact list of original studies) and were queried as to whether they were aware of ongoing RCTs that met our inclusion criteria; two more RCTs were thus identified [19,20]. No study protocol for this study has been developed.

Risk-of-bias assessment and data extraction

Five criteria from the Cochrane Collaboration risk-of-bias assessment tool were applied (by EK, HR, and NBo): (1) adequate random sequence allocation, (2) concealment of allocation to the different conditions, (3) blinding of participants and therapists to the study condition, (4) blinding of assessors to outcomes, and (5) handling of missing data [21].

IPDMA

Primary outcome measure. The primary outcome was mean weekly alcohol consumption, expressed in standard units. As RCTs differ in the quantification of alcohol in beverages, based on national custom (ranging from 8 to 14 grams of ethanol per unit [22]), we recalculated these into standard units of alcohol consumption based on 10 grams of ethanol (SUs). Most RCTs measured alcohol consumption using time line follow-back (TLFB) approaches. For a few RCTs that did not report TLFB data, we estimated mean weekly SUs on the basis of

the first two questions of The Alcohol Use Disorders Identification Test (brief, 3 items; AUDIT-C) scale [23] at post-intervention. Alcohol consumption at baseline was constructed identically. Most included participants were regular drinkers who were consuming more than the recommended low-risk weekly limits of 14 SUs (females) or 21 SUs (males) at baseline. Binge-only drinking is another problem drinking profile in which low-risk recommendations are exceeded. We defined binge-only drinkers by proxy as participants who drank more than 4 or 6 SUs (females/males) on at least one occasion per week, while still totalling less than 14/21 SUs weekly.

Secondary outcome measure. Treatment response (TR) was defined as an alcohol consumption level below 14/21 SUs per week for females/males at the first post-intervention follow-up.

Moderators. The following participant-level putative moderators were tested: gender (female/male); age (below 55/above 55); education (high/low, with 'high' referring to tertiary education and 'low' to primary or secondary schooling), employment (yes/no), and partner relationship (yes/no). Two dimensions of problem drinking were explored: regular drinking (>14/21 SUs female/male weekly) as contrasted with binge-only drinking (≥4/6 SUs female/male at least once a week but below 14/21 female/male SUs weekly); and heavy drinking (>35/50 SUs female/male weekly) as contrasted with non-heavy drinking (14–35 SUs weekly in females and 21–50 SUs weekly in males). Intervention-level putative moderators were therapeutic guidance (human-guided versus unguided interventions), intensity (single versus multiple sessions), therapeutic orientation (PNF-only versus integrated therapeutic principles), and intervention setting (in work, healthcare, or community populations). A study design moderator, type of control, was also included (waitlist control contrasted with assessment-only or minimal-intervention control).

One-stage and two-stage IPDMAs. Replications of individual study outcomes based on the raw data in comparison with the published results led to only one correction to the published tables [24]. We next applied a one-stage individual patient data (IPD) model of analysis, as it is assumed to produce a more exact likelihood specification than a two-stage approach [25]. In a one-stage IPDMA, the effect of iAIs is evaluated by fitting a single comprehensive model to the IPD from all trials, while simultaneously accounting for the nesting of participants within these trials. To account for the nesting structure, we assessed the summary effect of iAIs on the primary outcome using a linear mixed model (LMM). At the participant level, we used an ANCOVA model [26], regressing the post-intervention outcome score on the iAI intervention indicator, with the baseline alcohol consumption score used as a covariate.

To deal with missing baseline alcohol data, we used mean imputation to estimate scores [27]. We subsequently analysed all available outcomes using complete cases—that is, including the full baseline outcomes (N = 14,198) but ignoring missing post-intervention outcomes. This analysis implicitly assumes that the missing data are missing at random (MAR) rather than missing completely at random (MCAR), allowing missingness of post-intervention scores to depend on the pre-intervention score.

To evaluate the effect of iAIs using an LMM, we regressed the post-intervention weekly SU level on the iAI intervention indicator, the baseline weekly SU level, and the comparison indicators (dummy variables contrasting the intervention arms with the control arms of the trials), assuming random effects (both intercepts and intervention slopes) for those comparisons and equal residual variances across trials. The estimates of the iAIs' effects are presented as unstandardised regression coefficients (b), which refer to the overall effect of the intervention on posttreatment drinking behaviour in terms of comparative SU levels.

For TR, a generalised LMM with participants nested within trials (a logistic model) was similarly used. TR at follow-up (yes/no) was the dichotomous dependent variable, and all fixed

and random effects were identical to those in the LMM for the continuous primary outcome, except that fixed intercepts were removed for reasons of identification (convergence), resulting in a model with random intercepts (and slopes). We calculated odds ratios (ORs), representing the probability that an outcome will occur given a particular exposure as compared with the probability in the absence of that exposure [28]. TR was additionally interpreted by transforming the OR to a number needed to treat (NNT) [29].

We subsequently tested whether participant, intervention, or study design characteristics moderated the effect of iAIs on either the primary or the secondary outcome or both. However, participant-level characteristics and study- and intervention-level characteristics were analysed differently. For participant-level characteristics, within-study and across-study interaction effects had to be separated to avoid ecological bias [25], whilst no such separation was needed for study- and intervention-level moderators. We additionally performed two-stage analyses to evaluate the sensitivity of the one-stage results, a recommendation by Burke and colleagues [25]. The two-stage approach in our study derived aggregate data for effect estimates and their CIs for each study individually (step one), then combined these in a conventional meta-analysis model (step two). In two-stage analyses, participant-level moderators are estimated for each study separately and combined in the second stage, without risk of ecological bias, while intervention- and study-level characteristics are studied by comparing subgroups of trials in the second stage.

In the one-stage approach, we added a second sensitivity analysis to compare our results against those of a procedure applying multiple imputation to include all participants (an intention-to-treat [ITT] analysis). This analysis was conducted on the request of one of the reviewers. The multiple imputation procedure used chained equations to impute missing alcohol consumption scores—both before and after the intervention—together with missing values of the participant-level putative moderators. The ITT analysis employed logistic regression models for the dichotomous variables and predicted-mean matching for the continuous variables, with study indicators and intervention indicators (fully interacted) included as covariates. This second sensitivity analysis tested the main intervention effect and the moderator effects of all participant-level and study-level moderators on the primary outcome variable.

In the two-stage approach, we employed a third sensitivity analysis that evaluated the MAR assumption on the missing data mechanism, thereby answering an additional question of one of the reviewers. This additional, missing-not-at-random (MNAR) analysis is part of the ITT strategy suggested by White and colleagues [30]; it includes all randomised individuals in the analysis, taking baseline outcomes of dropouts into account. It evaluates a series of values of a sensitivity parameter δ, which equals the difference between the mean of the observed values of post-intervention SUs of alcohol and the mean of the unobserved values. Under MAR, δ (being the covariate-adjusted mean difference between missing and observed outcomes) is assumed to be zero. In our case, positive (or negative) values of δ correspond to the situation in which the dropouts, after adjustment for pre-intervention SUs, would have higher (or lower) mean values of post-intervention SUs than those who continued participation (see S1 Text for a detailed explanation of the evaluation of the MAR assumption). This third sensitivity analysis targeted the main intervention effect on the primary outcome variable only.

To examine heterogeneity, we calculated the I^2 statistic using the two-stage approach as well. This indicator is expressed as a percentage: an I^2 value of 0% is interpreted as no heterogeneity, 25% as low, 50% as moderate, and 75% as high heterogeneity [31]. We calculated the 95% CIs around I^2 using the noncentral chi-squared–based approach within the heterogeneity module for Stata [32,33]. All analyses were conducted with Stata 14.2.

Comparison of IPDMA-included with non-included RCTs

The potential differences in treatment outcomes between the trials included and those that could not be included in preparing our IPDMA were assessed with a conventional meta-analysis (Comprehensive Meta-Analysis, version 3.3.070; S3 Data).

Results

Results are reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses for IPD (S1 PRISMA Checklist) [34].

Selection of RCTs

Fig 1 illustrates the selection process for the trials included in our IPDMA. We identified 183 full papers, from which 24 eligible RCTS were found, five of which [35–39] could not be included (all involving unguided iAIs) because authors did not respond to our invitation.

Study characteristics

Table 1 shows the characteristics of the 19 included RCTs (26 comparisons). Most trials applied the full Alcohol Use Disorders Identification Test (AUDIT) (*n* = 9, cutoff ≥8) [40] or AUDIT-C scales (*n* = 4, cutoff ≥4 or ≥5) [23] as inclusion criteria. Four RCTs used cutoff thresholds based on daily or weekly low-risk drinking recommendations; the Fast Alcohol Screening Test (FAST) was applied in two trials [41]. Participants were recruited either directly
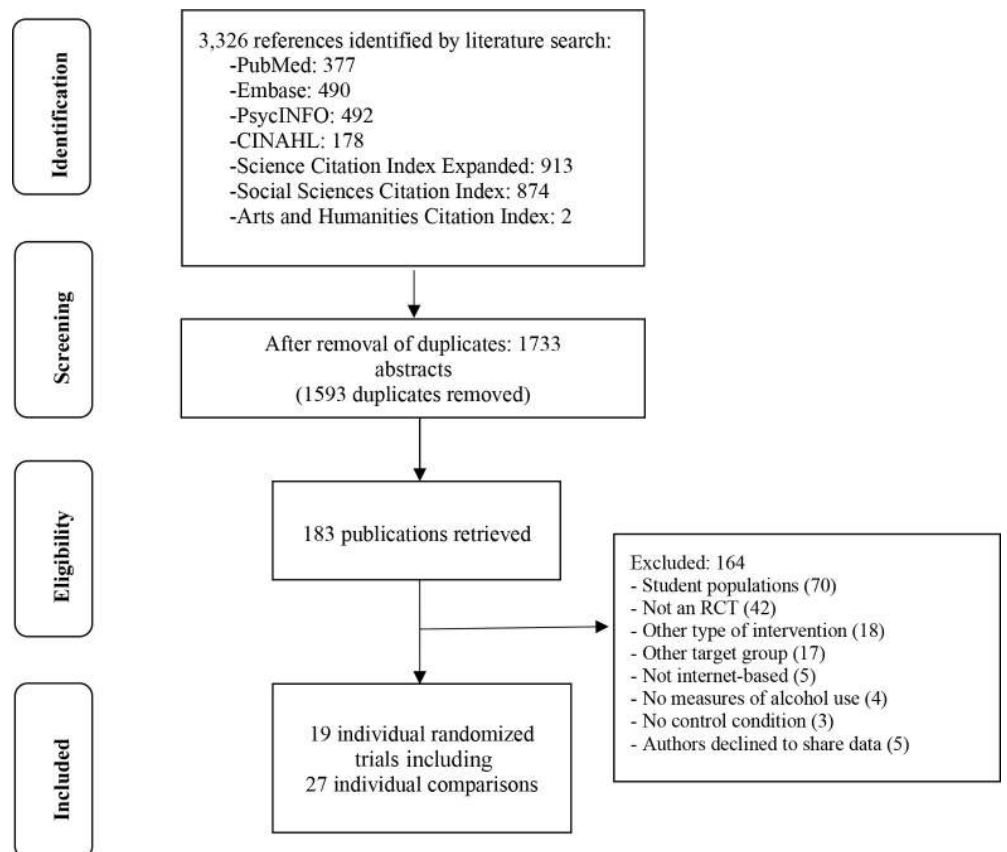

Fig 1. PRISMA IPD diagram of RCTs selection process. IPD, individual patient data; RCT, randomised controlled trial.

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Table 1. Characteristics of studies analysed in IPDMA (19 studies, 27 comparisons).

Study	Target group/Screener	Setting/Recruitment	Intervention	Mode of delivery	N	Control	Timing of FPTA
Araki et al. 2006 / JP [42]	Males >20 g ethanol/day, abnormal serum γ-GT	Workplace	Alcohol psychoeducation—MSG	Email	24	Waitlist	2 months
Bertholet et al. 2015 / CH [43]	Males age 21, AUDIT score >8 or >140 g ethanol/week; ≥60 g/occasion	General population cohort, army conscription centres	PNF extended—SSU	Internet	737	Assessment-only	1 month
Bischof et al. 2008 / DE [44]	AUDIT >5, LAST ≥2	General practices	a) TTM/BCC/MI: SC: digital + brief phone feedback—MSG	Digital + phone	408	Health behaviour booklet	12 months
			b) TTM/BCC/MI: Full: digital + longer phone feedback—MSG				
Blankers et al. 2011 / NL [45]	AUDIT >8 and >140 g ethanol/week	Community and SATC	a) CBT/MI—MSU	Internet	205	Waitlist	3 months
			b) CBT/MI—MSG				
Boon et al. 2011 / NL [46]	Males >200 g ethanol/week and/or >50 g ethanol on ≥1 day/week	Community	PNF—SSU	Internet	450	Alcohol leaflet	1 month
Boß et al. (2017) / DE [47]	F/M AUDIT score >6/8 and F/M >140/210 g ethanol/week	Community	a) PNF/MI/BA—MSG	Internet	432	Waitlist	1.5 months
			b) PNF/MI/BA—MSU				
Brendryen et al. 2014 / NO [48]	FAST ≥3	Community	PNF/BSC/CBT—MSU	Internet	244	PNF/SSU/e-booklet	2 months
Brendryen et al. 2017 / NO [20]	FAST ≥3	Workplace	PNF/ /BSC/CBT—MSU	Internet	85	PNF/SSU/e-booklet	2 months
Cunningham et al. 2009 / CA [49]	AUDIT-C ≥4	Community	PNF—SSU	Internet	72	Alcohol leaflet	3 months
Hansen et al. 2012 / DK [50]	F/M >140/210 g ethanol/week	Community	PNF—SSUPBA—SSU	Internet	761	Assessment-only	6 months
Hester et al. 2005 / US [51]	AUDIT ≥8	Community	PNF/BSC/MI—SSU	CD-ROM; healthcare setting	61	Waitlist	1 month
Khadjesari et al. 2014 / UK [52]	AUDIT-C ≥5	Workplace	PNF/SC—SSU	Internet	1,330	Assessment-only	3 months
Postel et al. 2010 / NL [53]	F/M ≥150/220 g ethanol/week with upper limit of F/M <670/990 g	Community and SATC	CBT/MI—MSG	Internet	156	Waitlist	3 months
Riper et al. 2008 / NL [54]	F/M >140/210 g ethanol/week or F/M ≥40/60 g ethanol/≥1 day in past 3 months	Community	CBT/BSC/MI—MSU	Internet	261	e-Alcohol leaflet	6 months
Schulz et al. 2013 / DE [55]	AUDIT >7[1] or F/M >10/20 g ethanol/day or drinking >5 days/week	Community	Alternating versus summative PNF—MSU	Internet	498	Assessment-only	6 months
Sinadinovic et al. 2014 / SE [56]	F/M AUDIT ≥6/8	Community	PNF/CBT/MI—MSU	Internet	633	Assessment-only	3 months
			PNF/CBT/MI—SSU				
Suffoletto et al. 2012 / US [57]	F/M AUDIT-C ≥3/4 in past 3 months	Emergency department	PNF—MSU with monitoring only PNF—MSU	SMS	45	Assessment-only	3 months
Sundström et al. 2016 / SE [58]	F/M AUDIT ≥6/8	Community/web	a) CBT/BSC/MI—MSG asynchronous	Internet	80	Web-based unguided self-help	2.5 months
			b) CBT/BSC/MI—MSG synchronous				

(Continued)

Table 1. (Continued)

Study	Target group/Screener	Setting/Recruitment	Intervention	Mode of delivery	N	Control	Timing of FPTA
Wallace et al. 2011 / UK [59]	AUDIT-C ≥5	Community/web	CBT/BSC/MI—MSU	Internet	1,281[2]	Unguided noninteractive web psychoeducation	3 months

[1]Only participants scoring ≥8 on AUDIT were included in IPDMA.

[2]Main trial.

Abbreviations: γ-GT, gamma-glutamyltransferase; AA, alcohol abuse; AD, alcohol dependence; AR, at-risk drinking; AUDIT, Alcohol Use Disorders Identification Test; AUDIT-C, Alcohol Use Disorders Identification Test–Consumption; BA, behavioural activation; BCC, behavioural change counselling; BSC, behavioural self-control training; CA, Canada; CBT, cognitive-behavioural therapy; CD-ROM, Compact Disc, read-only-memory; CH, Switzerland; DE, Germany; DK, Denmark; FAST, Fast Alcohol Screening Test (≥3 indicates problem drinking); F/M, female/male; FPTA, first posttreatment assessment; G, human-guided; HDE, heavy drinking episode; IPDMA, individual patient data meta-analysis; JP, Japan; LAST, Luebeck Alcohol Dependence and Abuse Screening Test; M-CIDI, Munich Composite International Diagnostic Interview; MI, motivational interviewing; MSG, multiple-session guided; MSU, multiple-session unguided; NL, Netherlands; NO, Norway; PBA, personalised brief advice intervention; PNF, personalised normative feedback; SATC, substance abuse treatment centre; SC, stepped care; SE, Sweden; SMS, Short Message Service; SSU, single-session unguided; TTM, Transtheoretical Model of Behavioral Change; UK, United Kingdom; US, United States; web, world wide web.

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from the community ($n = 12$ trials), from healthcare settings ($n = 4$), or from work settings ($n = 3$). Eight trials employed a minimal-intervention control design, six trials applied assessment-only control, and five included a waitlist-control comparator. Eleven trials estimated the effects of multiple-session iAIs, seven studied single-session iAIs, and one study included both types. Twelve investigated effects of therapeutically integrated iAIs and seven studied PNF-only interventions. Most comparisons ($n = 19$) involved unguided iAIs; eight involved human-guided interventions. The first post-intervention assessment occurred in most trials ($n = 15$) between 1 and 3 months after treatment, in three trials at 6 months, and in one study at 12 months. A total of $N = 14,198$ participants was included, out of the 17,545 participants in the 24 identified trials (a 79.77% inclusion rate).

Participants' characteristics at baseline

Of the total of 14,198 enrolled participants, 8,095 provided post-intervention outcome data (complete cases, Table 2). The mean age of the overall sample was 40.7 (SD = 13.2) and the sample was rather evenly divided by gender (47.6% women, 52.4% men). Some 51.9% of participants had tertiary education, 74.8% had paid employment, and 56.7% were in partner relationships. The mean weekly SU level at baseline was 38.1 (SD = 26.9). Most problem drinkers (80.1%, SUs 44.7, SD = 26.4) could be categorised as regular drinkers and 19.9% (SUs 11.9, SD = 4.1) as binge-only drinkers. Regular drinkers could be distinguished into heavy drinkers (34.2%, SUs 65.9, SD = 27.1) and non-heavy drinkers (65.8%, SUs 23.7, SD = 10.6). Heavy drinkers were found in both unguided and guided iAIs (34% and 30%, respectively). The mean full AUDIT score ($n = 9$ trials) was 15.0 (SD = 6.8), indicating hazardous or harmful alcohol use [40]. Of the participants for which a full AUDIT score was available, 22.2% ($n = 678$) scored above 20, indicating a risk of alcohol dependence. Missing SU scores at baseline were virtually nil (0.4%). Missing data at the first post-intervention assessment for the primary outcome were considerable (43%), predominantly resulting from study dropout, which was not entirely random: participants under age 55 and those with baseline heavy-drinking profiles dropped out significantly more than others.

Risk of bias

The quality of the RCTs was relatively high (Fig 2 and S1 Table). All but one scored high-risk on the blinding of participants, which was expected, as this criterion is difficult to meet for

Table 2. Characteristics of all study participants at baseline (*n* = 14,198) and complete cases (*n* = 8,095).

Baseline participant characteristics	All respondents			Complete cases		
	Males	Females	Total	Males	Females	Total
	7,443	6,755	14,198	4,437	3,658	8,095
	(52.4%)	(47.6%)	(100%)	(54.8%)	(45.2%)	(100%)
Age (SD)	41.0	40.4	40.7	41.6	41.7	41.6
	(14.1)	(12.2)	(13.2)	(14.8)	(12.4)	(13.8)
Education** tertiary (yes)	2,785/5,440	3,095/5,895	5,880/11,335	1,520/2,901	1,719/3,117	3,239/6,018
	51.2%	52.5%	51.9%	52.4%	55.1%	53.8%
Employed (yes)**	2,095/2,774	1,203/1,634	3,298/4,408	1,557/2,034	859/1,145	2,416/3,179
	75.5%	73.6%	74.8%	76.5%	75.0%	76.0%
Partner (yes)**	3,567/5,985	3,222/5,999	6,789/11,984	2,051/3,314	1,742/3,182	3,793/6,496
	59.6%	53.7%	56.7%	61.9%	54.7%	58.3%
SU/week at baseline (SD)	41.0	35.0	38.1	35.8	32.1	34.1
	(29.9)	(22.8)	(26.9)	(27.2)	(20.9)	(24.6)
Problem-drinking profiles						
Patterns						
Regular drinking*	5,488	5,878	11,366	2,970	3,112	6,082
	73.7%	87.0%	80.1%	66.9%	85.1%	75.1%
SU (SD)^1	51.0	38.8	44.7	47.2	36.1	41.5
	(28.7)	(22.1)	(26.2)	(26.5)	(20.2)	(24.1)
Binge-only drinking	1,955	877	2,832	1,467	546	2,013
	26.3%	13.0%	19.9%	33.1%	14.9%	24.9%
SU (SD)^2	13.0	9.5	11.9	12.8	9.5	11.9
	(4.1)	(2.8)	(4.1)	(4.1)	(2.8)	(4.1)
Quantities						
Heavy drinkers	2,142	2,707	4,849	977	1,283	2,260
	28.8%	40.1%	34.2%	22.0%	35.1%	27.9%
SU (SD)	78.6	55.9	65.9	76.4	53.7	63.5
	(27.7)	(21.9)	(27.1)	(27.2)	(20.6)	(26.2)
Non-heavy drinkers	5,301	4,048	9,349	3,460	2,375	5,835
	71.2%	59.9%	65.8%	78.0%	64.9%	72.1%
SU (SD)	25.8	21.0	23.7	24.3	20.5	22.8
	(11.9)	(7.9)	(10.6)	(11.8)	(7.8)	(10.6)
AUDIT	14.2	16.6	15.0	13.4	15.6	14.1
(SD)	(6.6)	(6.7)	(6.8)	(6.2)	(6.4)	(6.4)
(*n* of studies)	9	7	9	8	7	8
(*n* of participants)	2,027	975	3,002	1,625	658	2,283
Dropout						
All	3,006	3,097	6,103			
	40.4%	45.8%	43.0%			
Age ≥ 55	460/1,460	321/881	781/2,341			
	31.5%	36.4%	33.4%			
Binge-only drinkers	488/1,955	331/877	819/2,832			
	25.0%	37.7%	28.9%			
Heavy drinkers	1,165/2,142	1,424/2,707	2,589/4,849			
	54.4%	52.6%	53.4%			

(*Continued*)

Table 2. (Continued)

Baseline participant characteristics	All respondents			Complete cases		
	Males	Females	Total	Males	Females	Total
Follow-up data available	4,437	3,658	8,095			

*Outliers above 175 SUs per week were set at 175 SUs (*n* = 23 participants at baseline).

**These variables were not assessed in all studies, therefore the numerator and denominator are listed here separately.

[1]Regular drinking denotes 14 or more SUs weekly for females or 21 or more for males (thus excluding binge-only drinking).

[2]Binge-only drinking denotes more than 4 or 6 SUs (females/males) on at least one occasion per week, while still totalling less than 14/21 SUs weekly.

Abbreviations: AUDIT, The Alcohol Use Disorders Identification Test; SU, standard unit of alcohol consumption based on 10 grams of ethanol.

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behavioural change trials. All trials included ITT analyses, but seven had a high bias risk in terms of high study dropout (over 30%).

One-stage IPDMA analyses: Main outcomes

The overall difference in mean weekly alcohol reduction was significant and in favour of the iAI condition (*b* = −5.02 SUs, 95% CI −7.57 to −2.48, *p* < 0.001; see Table 3). We identified four outliers (RCTs in which the 95% CI did not overlap with that of our pooled effect size) [43,52,53,59]. Removal of these outliers altered the result only slightly (*b* = −4.81 SUs, 95% CI −6.69 to −2.93, *p* < 0.001). For two trials (Khadjesari 2014, *N* = 1,330, and Sinadinovic 2014, *N* = 633), we had estimated the mean weekly SUs on the basis of the first two questions of the AUDIT-C; removal of those trials likewise only slightly altered the result (*b* = −5.74 SUs, 95% CI −8.55 to −2.92, *p* < 0.001).

iAI participants also had a significantly greater likelihood of TR than controls (OR = 2.20, 95% CI 1.63–2.95, *p* < 0.001, NNT = 4.15, 95% CI 3.06–6.62), which remained after removal of the outliers (OR = 2.15, 95% CI 1.67–2.77, *p* < 0.001; see Table 4) or the two AUDIT-estimated trials (OR = 2.50, 95% CI 1.81–3.45, *p* < 0.001; see Table 4). Follow-up periods in the analysis were different, but they were not associated with outcomes (primary *p* = 0.41, secondary *p* = 0.12).

Moderator analyses

Participant characteristics. Both men and women treated in iAIs decreased their mean weekly SU levels to a greater degree than controls, but women did so less than men (2.19 SUs, 95% CI 0.52–3.85, *p* = 0.013). Additional sensitivity analyses maintained this difference. In the
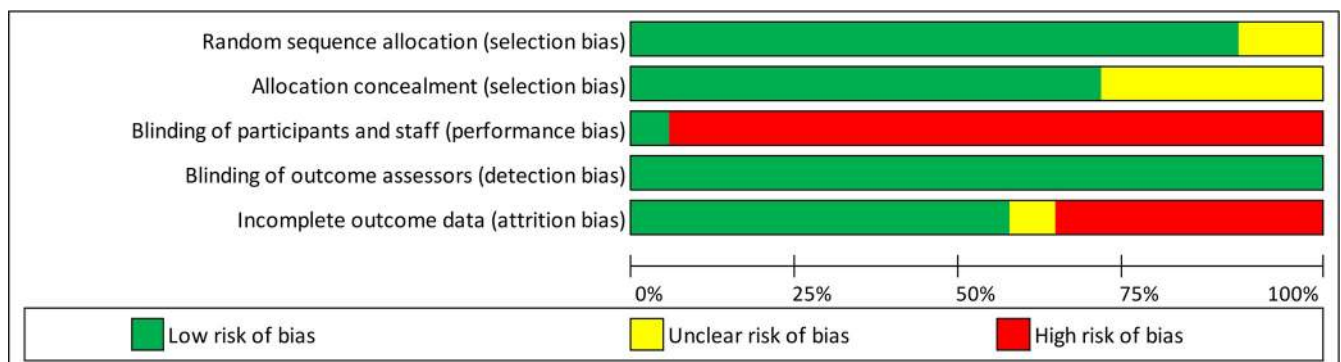

Fig 2. Risk-of-bias assessment.

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Table 3. Effects of iAIs in terms of weekly SUs, moderating effects, and subgroup analyses (one- and two-stage results).

Primary outcome (SUs) and outcome moderators	Comparisons	Persons[5]	One-Stage Results			Two-Stage Results		
			Effect[6]	95% CI	p-value	Effect[6]	95% CI	p-value
Overall effect	**27**	**8,095**	*b = −5.02 SU*	**(−7.57, −2.48)**	**<0.001**	*b = −4.80 SU*	**(−6.99, −2.61)**	**<0.001**
With outlier studies removed[1]	**23**	**3,129**	*b = −4.81 SU*	**(−6.69, −2.93)**	**<0.001**	*b = −4.36 SU*	**(−5.93, −2.78)**	**<0.001**
With studies with AUDIT-only estimates removed[2]	**24**	**6,909**	*b = −5.74 SU*	**(−8.55, −2.92)**	**<0.001**	*b = −5.54 SU*	**(−7.99, −3.09)**	**<0.001**
Participant-level characteristics								
Sociodemographics								
Gender (female)	**27**	**8,095**	*b = 2.19 SU*	**(0.52, 3.85)**	**0.010**	*b = 1.56 SU*	(−0.06, 3.19)	0.059
Age (55 or older)	26	8,071	*b = −1.62 SU*	(−3.72, 0.48)	0.130	*b = −1.56 SU*	(−3.10, −0.02)	0.047
Education (high)	18	**6,018**	*b = 2.12 SU*	**(0.18, 4.07)**	**0.033**	*b = −0.08 SU*	(−2.83, 2.68)	0.955
Employment (yes)	16	3,179	*b = −0.30 SU*	(−2.67, 2.07)	0.804	*b = −0.51 SU*	(−2.93, 1.92)	0.682
Partner relationship (yes)	13	6,496	*b = −0.51 SU*	(−2.30, 1.28)	0.576	*b = −0.45 SU*	(−1.92, 1.01)	0.544
Drinking profiles								
Regular versus binge-only drinking[3]	27	8,095	*b = −0.99 SU*	(−3.19, 1.21)	0.376	*b = −0.15 SU*	(−1.67, 1.38)	0.851
Quantity								
Heavy versus non-heavy drinking[4]	27	8,095	*b = −1.50 SU*	(−3.35, 0.36)	0.114	*b = −6.03 SU*	(−10.23, −1.84)	0.005
Intervention-level characteristics								
Therapeutic guidance								
Unguided	**19**	**7,366**	*b = −3.23 SU*	**(−5.88, −0.59)**	**0.017**	*b = −2.55 SU*	(−4.06, −1.04)	0.001
Guided	**8**	**729**	*b = −10.01 SU*	**(−14.64, −5.39)**	**<0.001**	*b = −10.68 SU*	(−16.80, −4.57)	0.001
Contrast: Guided versus Unguided			*b = −6.78 SU*	**(−12.11, −1.45)**	**0.013**	*b = −8.14 SU*	(−14.44, −1.84)	0.011
Intensity								
Single session	11	3,050	*b = −3.73 SU*	(−7.71, 0.24)	0.066	*b = −2.97 SU*	(−5.14, −0.79)	0.008
Multiple sessions	**16**	**5,045**	*b = −5.96 SU*	**(−9.31, −2.60)**	**0.001**	*b = −6.07 SU*	(−9.55, −2.60)	0.001
Contrast: Multiple versus Single			*b = −2.22 SU*	(−7.43, 2.98)	0.402	*b = −3.11 SU*	(−7.21, 1.00)	0.138
Therapeutic orientation								
Integrated	**18**	**5,550**	*b = −6.53 SU*	**(−9.57, −3.49)**	**<0.001**	*b = −6.65 SU*	(−9.77, −3.53)	<0.001
PNF only	9	2,545	*b = −1.98 SU*	(−6.24, 2.28)	0.363	*b = −1.71 SU*	(−3.68, 0.27)	0.091
Contrast: PNF versus Integrated			*b = 4.55 SU*	(−0.68, 9.79)	0.088	*b = 4.94 SU*	(1.25, 8.64)	0.009
Intervention setting								
Work	3	973	*b = −1.88 SU*	(−9.52, 5.76)	0.630	*b = −2.69 SU*	(−7.61, 2.24)	0.285
Healthcare	**7**	**612**	*b = −9.12 SU*	**(−14.33, −3.90)**	**0.001**	*b = −8.08 SU*	(−15.88, −0.28)	0.042
Community	**17**	**6,510**	*b = −4.12 SU*	**(−7.04, −1.19)**	**0.006**	*b = −3.50 SU*	(−5.29, −1.70)	<0.001
Study-level characteristics								
Type of control								
Waitlist (WLC)	**7**	**647**	*b = −11.86 SU*	**(−16.01, −7.71)**	**<0.001**	*b = −11.57 SU*	(−17.83, −5.30)	<0.001
Other (AOC or MIC)	**20**	**7,448**	*b = −2.59 SU*	**(−4.81, −0.38)**	**0.022**	*b = −2.44 SU*	(−3.94, −0.95)	0.001
Contrast: WLC versus Other			*b = −9.27 SU*	**(−13.97, −4.57)**	**<0.001**	*b = −9.12 SU*	(−15.56, −2.68)	0.005
Assessment only (AOC)	10	2,811	*b = −0.96 SU*	(−4.05, 2.12)	0.541	*b = −0.88 SU*	(−2.16, 0.39)	0.175
Waitlist (WLC)	**7**	**647**	*b = −11.86 SU*	**(−16.01, −7.71)**	**<0.001**	*b = −11.57 SU*	(−17.83, −5.30)	<0.001
Minimal intervention (MIC)	**10**	**4,637**	*b = −4.33 SU*	**(−7.51, −1.15)**	**0.008**	*b = −4.98 SU*	(−7.88, −2.07)	0.001
Interactions								
Unguided with WLC	**3**	**307**	*b = −8.25 SU*	**(−14.16, −2.33)**	**0.006**	*b = −6.59 SU*	(−11.57, −1.61)	0.009
Unguided with Other control	16	7,059	*b = −2.24 SU*	(−4.53, 0.07)	0.057	*b = −2.10 SU*	(−3.62, −0.57)	0.007
Contrast: Unguided—WLC versus Other control			*b = −6.01 SU*	(−12.36, 0.34)	0.063	*b = −4.49 SU*	(−9.70, 0.71)	0.091
Guided with WLC	**4**	**340**	*b = −14.96 SU*	**(−20.47, −9.44)**	**<0.001**	*b = −14.11 SU*	(−23.68, −4.55)	0.004
Guided with Other control	4	389	*b = −4.45 SU*	(−10.06, 1.17)	0.121	*b = −5.68 SU*	(−10.51, −0.84)	0.021

(*Continued*)

Table 3. (Continued)

Primary outcome (SUs) and outcome moderators	Comparisons	Persons[5]	One-Stage Results			Two-Stage Results		
			Effect[6]	95% CI	p-value	Effect[6]	95% CI	p-value
Contrast: Guided—WLC versus Other control			**b = −10.51 SU**	**(−18.38, −2.64)**	**0.009**	b = −8.43 SU	(−19.15, 2.28)	0.123

Significant results are shown in **bold**.

Other control = MIC or AOC.

[1]Studies 36–39 were regarded as outlier studies.

[2]These were studies [52,56].

[3]Regular drinking denotes 14 or more SUs weekly for females or 21 or more for males (thus excluding binge-only drinking). Binge-only drinking denotes more than 4 or 6 SUs (females/males) on at least one occasion per week while still totalling less than 14/21 SUs weekly.

[4]Heavy drinking denotes 35 or more SUs weekly for females and 50 or more for males; non-heavy drinking denotes 14/21 SUs or more, but less than 35/50 SUs, weekly for females/males.

[5]The number of persons refers to respondents for whom data were available on post-intervention drinking behaviour (complete cases) and, for the participant level, also on the moderator in question.

[6]Unstandardised regression coefficients (b) indicate the effect of the iAIs in terms of alcohol reduction in SUs.

Abbreviations: AOC, assessment-only control; AUDIT, The Alcohol Use Disorders Identification Test; iAI, internet-based alcohol intervention; MIC, minimal-intervention control (e.g., information brochure); PNF, personalised normative feedback; SU, standard units of alcohol; WLC, waitlist control; 95% CI, 95% confidence interval.

first analysis we included only men and women who were exceeding 14 SUs of alcohol at baseline and found a moderator effect of $b = 2.36$ (95% CI 0.41–4.31, $p = 0.018$) for female gender. In the second analysis we included males and females who were exceeding 21 SUs at baseline, resulting in a very similar difference of $b = 2.52$ (95% CI 0.22–4.82, $p = 0.031$). A comparable result emerged for higher- versus lesser-educated participants (2.12 SUs smaller reduction for the former, 95% CI 0.18–4.0, $p = 0.033$). Participants above age 55 were significantly more likely to show TR than younger participants (OR = 1.68, 95% CI 1.22–2.30, $p = 0.001$). No other participant-level moderators were identified for the primary or the secondary outcome.

Intervention characteristics. Both unguided (−3.23 SUs, 95% CI −5.88–0.59, $p = 0.017$) and guided iAIs (−10.01 SUs, 95% CI −14.64 to −5.39, $p < 0.001$) were significantly more effective in reducing mean weekly SUs as compared with controls. Guided interventions were significantly more effective than unguided ones (−6.78 SUs, 95% CI −12.11 to −1.45, $p = 0.013$). Similar significant differences in favour of guided iAIs were seen in terms of TR (unguided: OR = 1.75, 95% CI 1.14–2.67, $p < 0.001$; guided: OR = 3.91, 95% CI 2.30–6.66, $p < 0.001$). Guided interventions positively moderated TR likelihood in comparison to unguided ones (OR = 2.23, 95% CI 1.22–4.08, $p = 0.009$). PNF-only interventions showed a significantly lower likelihood of TR than iAIs based on integrated therapeutic principles (OR = 0.52, 95% CI 0.29–0.93, $p = 0.029$). Intervention settings significantly moderated alcohol consumption outcomes for healthcare patients (−9.12 SUs, 95% CI −14.33 to −3.90, $p = 0.001$) and for community populations (−4.12 SUs, 95% CI −7.04 to −1.19, $p = 0.006$) but not for work populations. Similar significant results were evident for TR (healthcare: OR = 3.31, 95% CI 1.82–6.01, $p < 0.001$; community: OR = 2.07, 95% CI 1.50–2.85, $p < 0.001$).

Study design characteristics. Treatment participants in waitlist-controlled (WLC) trials significantly reduced their mean weekly alcohol consumption by greater amounts in comparison to controls than those treated in otherwise-controlled trials (−9.27 SUs, 95% CI −13.97 to −4.57, $p < 0.001$). Only the guided iAIs in WLC designs differed significantly from those in otherwise-controlled trials ($b = −10.51$ SUs, 95% CI −18.38 to −2.64, $p = 0.009$). iAI intervention participants in WLC trials were also significantly more likely to show favourable TR (OR = 3.74, 95% CI 2.13–6.53, $p < 0.001$) than those in other trials; significant differences were maintained for both

Table 4. Effects of iAIs in terms of TR (adherence to 14/21 guidelines), moderating effects, and subgroup analyses (one- and two-stage results).

Secondary outcome (TR) and outcome moderators	Comparisons	Persons[4]	One-Stage Results			Two-Stage Results		
			Effect	95% CI	*p*-value	Effect	95% CI	*p*-value
Overall effect	**27**	**6,082**	**OR = 2.20**	**(1.63, 2.95)**	**<0.001**	OR = 2.22	(1.58, 3.13)	<0.001
With outlier studies removed[1]	**23**	**2,490**	**OR = 2.15**	**(1.67, 2.77)**	**<0.001**	OR = 2.14	(1.66, 2.76)	<0.001
With studies with AUDIT-only estimates removed[2]	**24**	**5,527**	**OR = 2.50**	**(1.81, 3.45)**	**<0.001**	OR = 2.50	(1.72, 3.63)	<0.001
Participant-level characteristics								
Sociodemographics								
Gender (female)	27	6,082	OR = 1.00	(0.78, 1.27)	0.982	OR = 0.91	(0.70, 1.18)	0.495
Age (55 or older)	**26**	**6,065**	**OR = 1.66**	**(1.21, 2.27)**	**0.002**	OR = 1.61	(1.15, 2.26)	0.005
Education (high)	18	5,254	OR = 0.92	(0.71, 1.18)	0.493	OR = 1.17	(0.74, 1.86)	0.500
Employment (yes)	16	2,277	OR = 0.86	(0.54, 1.37)	0.535	OR = 0.98	(0.57, 1.68)	0.939
Partner relationship (yes)	14	5,279	OR = 0.96	(0.74, 1.24)	0.743	OR = 0.94	(0.72, 1.23)	0.673
Quantity								
Heavy versus non-heavy drinking[3]	27	8,095	OR = 0.94	(0.72, 1.23)	0.646	OR = 0.95	(0.71,1.28)	0.748
Intervention-level characteristics								
Therapeutic guidance								
Unguided	**19**	**5,544**	**OR = 1.75**	**(1.31, 2.35)**	**<0.001**	OR = 1.72	(1.29, 2.28)	<0.001
Guided	**8**	**538**	**OR = 3.91**	**(2.30, 6.66)**	**<0.001**	OR = 3.97	(1.61, 9.77)	0.003
Contrast: Guided versus Unguided			**OR = 2.23**	**(1.22, 4.08)**	**0.009**	OR = 2.31	(0.90, 5.94)	0.082
Intensity								
Single session	**11**	**1,817**	**OR = 1.75**	**(1.14, 2.67)**	**0.010**	OR = 1.66	(1.17, 2.35)	0.004
Multiple sessions	**16**	**4,265**	**OR = 2.58**	**(1.77, 3.75)**	**<0.001**	OR = 2.56	(1.56, 4.21)	<0.001
Contrast: Multiple versus Single			OR = 1.48	(0.84, 2.58)	0.172	OR = 1.54	(0.84, 2.83)	0.160
Therapeutic orientation								
Integrated	**18**	**4,819**	**OR = 2.67**	**(1.90, 3.76)**	**<0.001**	OR = 2.77	(1.79, 4.28)	<0.001
PNF only	9	1,263	OR = 1.40	(0.87, 2.25)	0.171	OR = 1.31	(0.93, 1.85)	0.122
Contrast: PNF versus Integrated			**OR = 0.52**	**(0.29, 0.93)**	**0.029**	OR = 0.47	(0.27, 0.83)	0.008
Intervention setting								
Work	3	359	OR = 1.23	(0.55, 2.75)	0.610	OR = 1.85	(0.46, 7.46)	0.387
Healthcare	**7**	**435**	**OR = 3.31**	**(1.82, 6.01)**	**<0.001**	OR = 3.08	(0.89, 10.63)	0.074
Community	**17**	**5,288**	**OR = 2.07**	**(1.50, 2.85)**	**<0.001**	OR = 1.95	(1.46, 2.60)	<0.001
Study-level characteristics								
Type of control								
WLC	**7**	**577**	**OR = 5.79**	**(3.51, 9.55)**	**<0.001**	OR = 5.42	(2.56, 11.46)	<0.001
Other (AOC or MIC)	**20**	**5,505**	**OR = 1.55**	**(1.20, 2.01)**	**0.001**	OR = 1.50	(1.18, 1.91)	0.001
Contrast: WLC versus Other			**OR = 3.74**	**(2.13, 6.53)**	**<0.001**	OR = 3.61	(1.64, 7.93)	0.001
AOC	10	1,529	OR = 1.31	(0.93, 1.86)	0.121	OR = 1.28	(0.96, 1.70)	0.091
WLC	**7**	**577**	**OR = 5.80**	**(3.48, 9.67)**	**<0.001**	OR = 5.42	(2.56, 11.46)	<0.001
MIC	**10**	**3,976**	**OR = 1.87**	**(1.28, 2.75)**	**0.001**	OR = 2.05	(1.28, 3.28)	0.003
Interactions								
Unguided with WLC	**3**	**276**	**OR = 3.71**	**(1.86, 7.40)**	**<0.001**	OR = 3.52	(1.90, 6.55)	<0.001
Unguided with Other control	**16**	**5,268**	**OR = 1.48**	**(1.15, 1.90)**	**0.002**	OR = 1.49	(1.15, 1.94)	0.003
Contrast: Unguided—WLC versus Other control			**OR = 2.51**	**(1.21, 5.22)**	**0.014**	OR = 2.36	(1.20, 4.62)	0.012
Guided with WLC	**4**	**301**	**OR = 8.46**	**(4.32, 16.58)**	**<0.001**	OR = 7.62	(2.30, 25.21)	0.001
Guided with Other control	4	237	OR = 1.59	(0.83, 3.06)	0.165	OR = 1.76	(0.75, 4.11)	0.195

(Continued)

Table 4. (Continued)

Secondary outcome (TR) and outcome moderators	Comparisons	Persons[4]	One-Stage Results			Two-Stage Results		
			Effect	95% CI	*p*-value	Effect	95% CI	*p*-value
Contrast: Guided—WLC versus Other control			**OR = 5.32**	**(2.08, 13.58)**	**<0.001**	OR = 4.34	(1.00, 18.85)	0.050

Significant results are shown in **bold**.

Other control = MIC or AOC.

[1]Studies 36–39 were regarded as outlier studies.

[2]These were studies [52,56].

[3]Heavy drinking denotes 35 or more SUs weekly for females and 50 or more SUs for males; non-heavy drinking denotes 14/21 SUs or more, but less than 35/50 SUs, weekly for females/males.

[4]The number of persons refers to respondents within the subsample of baseline regular drinkers for whom data were available on post-intervention drinking behaviour (complete cases) and, for the participant level, also on the moderator in question. Binge-only drinkers are excluded in this table, as these would have unjustifiably satisfied our mean weekly SU criterion for favourable TR.

Abbreviations: AOC, assessment-only control; AUDIT, The Alcohol Use Disorders Identification Test; iAI, internet-based alcohol intervention; MIC, minimal-intervention control (e.g., information brochure); PNF, personalised normative feedback; SU, standard unit of alcohol consumption based on 10 grams of ethanol; TR, treatment response; WLC, waitlist controlled; 95% CI, 95% confidence interval.

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unguided and guided iAIs with WLC designs as compared to other control (unguided: OR = 2.51, 95% CI 1.21–5.22, *p* = 0.014; guided: OR = 5.32, 95% CI 2.08–13.58, *p* < 0.001).

Sensitivity analyses

In the first sensitivity analysis, we checked the extent to which the results would be different if we used a two-stage approach instead of a one-stage approach. The second sensitivity analysis involved the inclusion of all participants according to the ITT principle by use of a multiple imputation strategy.

The third sensitivity analysis concerned the MAR assumption that is commonly used to deal with missing outcome data. All three of our sensitivity analyses confirmed the results of our main analysis for the overall effect and for most of the moderating effects of participant-, intervention-, and study-level characteristics for the primary and secondary outcomes. This appears to verify the robustness of our findings (see Tables 3 and 4 for the results of the two-stage approach and S2 Table and S3 Table, in which the results of the multiple imputation analyses are presented). Some minimal differences for moderators were seen in the multiple imputation analyses. The moderating role of gender and education for the primary outcome lost significance after multiple imputation. For the secondary outcome, the moderating role of single versus multiple sessions became significantly different in favour of multiple sessions, while intervention in the work setting became effective (*p* = 0.041), as was the case for assessment-only interventions. The contrast between PNF versus integrated iAIs became nonsignificant, as was the case for the contrast between unguided iAIs with WLCs versus other types of control conditions. Thus, in some cases these made our moderator analysis appear more conservative, while in some other cases the MI was more conservative.

Fig 3 depicts the results of the third, MNAR sensitivity analysis, which assessed departure from the MAR assumption. The figure shows estimates (and 95% CIs) of the overall intervention effect on our primary outcome variable, SU, for differing values of δ. The value of δ = 0 corresponds to the MAR assumption, on which the results displayed in Table 3 are based. Positive (or negative) values of δ correspond to situations in which—in each study included in the IPDMA and in both the intervention and the control arms—the mean of unobserved scores for post-intervention SUs would be higher (or lower) than the observed post-intervention SUs,
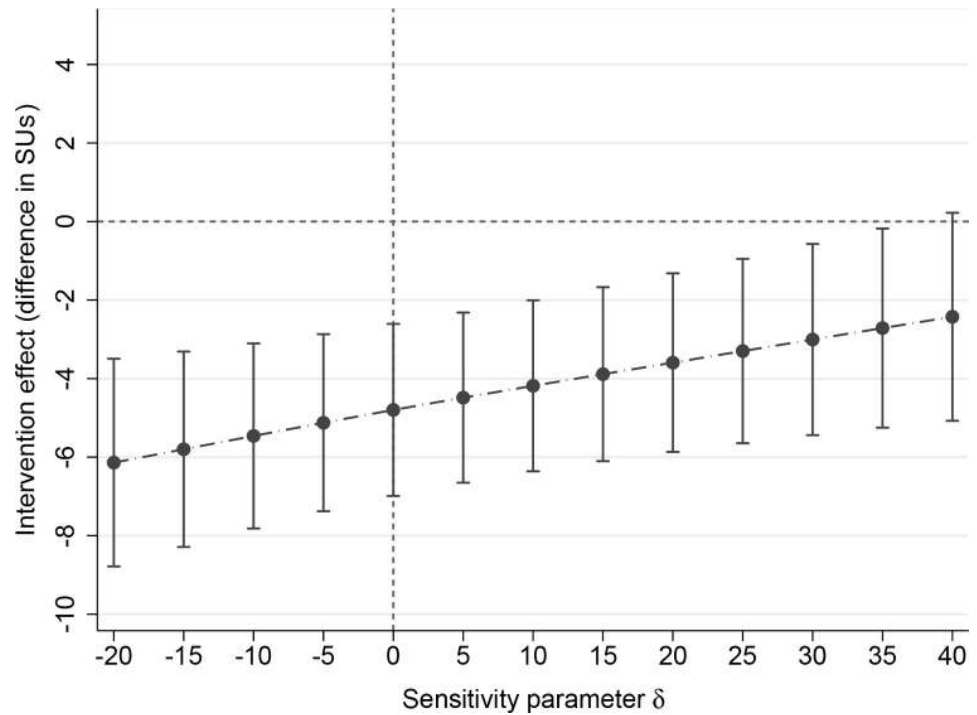
Fig 3. MNAR sensitivity analysis. MNAR, missing-not-at-random; SU, standard unit of alcohol consumption.

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after adjustment for pre-intervention SUs. If MAR holds, the overall effect is estimated in the two-stage method at −4.80 SU. Fig 3 shows that if the post-intervention SUs of dropouts, adjusted for the pre-intervention SUs, were to be 35 SUs higher on average than the post-intervention SUs of participants (being about 1.4 SD above the pre-intervention SUs shown in Table 2), then the estimate of the overall effect would be −4.06 SUs (95% CI −6.25–1.87). If the mean post-intervention SU level of dropouts were to be lower than those of participants (negative value of δ), then the overall effect would be stronger; for instance, if δ = −20, then the estimated overall effect would be −5.32 SUs (95% CI −7.64 to −3.01). This sensitivity analysis leads us to conclude that our results would remain rather stable, even in the event of substantial deviations from the MAR assumption (see S1 Text).

Heterogeneity for the overall primary outcome was high and significant (I^2 = 89.6%, CI 78.4%–95.2%, $p < 0.001$) and for the secondary outcome as well (I^2 = 78.2%, CI 56.3%–89.9%, $p < 0.001$). It could be partly explained by the identified outliers, as it dropped from high to moderate for the primary outcome (I^2 = 55.5%, CI 16.2%–80.3%, $p < 0.001$) and from high to small for the secondary outcome (I^2 = 30%, CI 0%–69.1%, $p < 0.001$) after removal of the outliers from the analyses (Tables 3 and 4).

Conventional meta-analysis comparing included with non-included RCTs

The conventional meta-analysis (24 trials, 34 comparisons) was based on our search up to 31 December 2016 and included additional data from two RCTs published in 2017 [20,47]. It revealed a small significant difference in mean weekly SUs at the first follow-up in favour of iAI participants as compared with controls (Hedges' g = 0.26, 95% CI 0.17–0.34, $p < 0.001$; Fig 4, forest plot of results of conventional meta-analysis). There was significant, moderate heterogeneity, indicating that the effect was greater in some trials than in others (I^2 = 65%, $p < 0.001$;

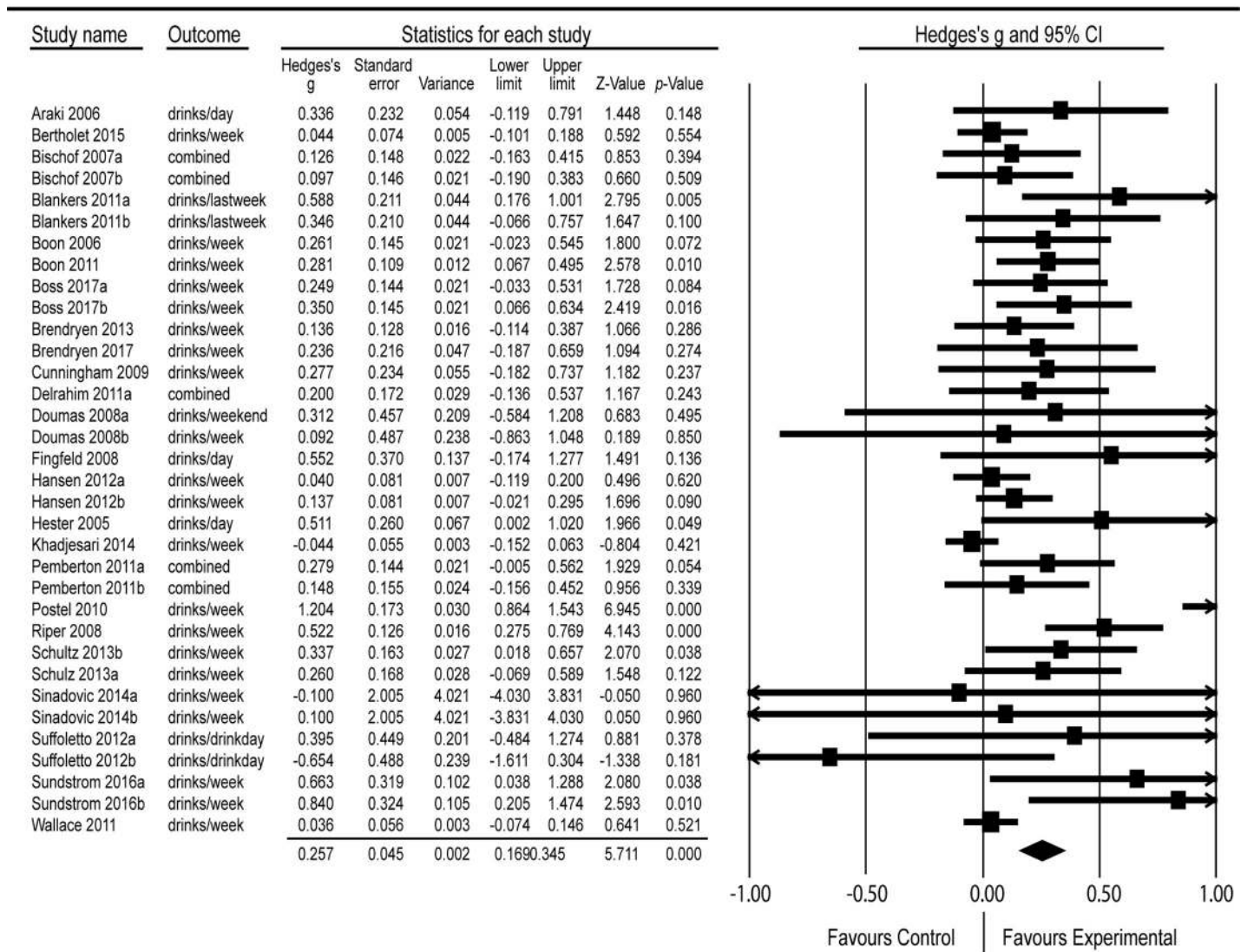## Forest plot of conventional meta-analysis iAi's versus controls

Study name	Outcome	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Hedges's g and 95% CI
Araki 2006	drinks/day	0.336	0.232	0.054	-0.119	0.791	1.448	0.148	
Bertholet 2015	drinks/week	0.044	0.074	0.005	-0.101	0.188	0.592	0.554	
Bischof 2007a	combined	0.126	0.148	0.022	-0.163	0.415	0.853	0.394	
Bischof 2007b	combined	0.097	0.146	0.021	-0.190	0.383	0.660	0.509	
Blankers 2011a	drinks/lastweek	0.588	0.211	0.044	0.176	1.001	2.795	0.005	
Blankers 2011b	drinks/lastweek	0.346	0.210	0.044	-0.066	0.757	1.647	0.100	
Boon 2006	drinks/week	0.261	0.145	0.021	-0.023	0.545	1.800	0.072	
Boon 2011	drinks/week	0.281	0.109	0.012	0.067	0.495	2.578	0.010	
Boss 2017a	drinks/week	0.249	0.144	0.021	-0.033	0.531	1.728	0.084	
Boss 2017b	drinks/week	0.350	0.145	0.021	0.066	0.634	2.419	0.016	
Brendryen 2013	drinks/week	0.136	0.128	0.016	-0.114	0.387	1.066	0.286	
Brendryen 2017	drinks/week	0.236	0.216	0.047	-0.187	0.659	1.094	0.274	
Cunningham 2009	drinks/week	0.277	0.234	0.055	-0.182	0.737	1.182	0.237	
Delrahim 2011a	combined	0.200	0.172	0.029	-0.136	0.537	1.167	0.243	
Doumas 2008a	drinks/weekend	0.312	0.457	0.209	-0.584	1.208	0.683	0.495	
Doumas 2008b	drinks/week	0.092	0.487	0.238	-0.863	1.048	0.189	0.850	
Fingfeld 2008	drinks/day	0.552	0.370	0.137	-0.174	1.277	1.491	0.136	
Hansen 2012a	drinks/week	0.040	0.081	0.007	-0.119	0.200	0.496	0.620	
Hansen 2012b	drinks/week	0.137	0.081	0.007	-0.021	0.295	1.696	0.090	
Hester 2005	drinks/day	0.511	0.260	0.067	0.002	1.020	1.966	0.049	
Khadjesari 2014	drinks/week	-0.044	0.055	0.003	-0.152	0.063	-0.804	0.421	
Pemberton 2011a	combined	0.279	0.144	0.021	-0.005	0.562	1.929	0.054	
Pemberton 2011b	combined	0.148	0.155	0.024	-0.156	0.452	0.956	0.339	
Postel 2010	drinks/week	1.204	0.173	0.030	0.864	1.543	6.945	0.000	
Riper 2008	drinks/week	0.522	0.126	0.016	0.275	0.769	4.143	0.000	
Schultz 2013b	drinks/week	0.337	0.163	0.027	0.018	0.657	2.070	0.038	
Schulz 2013a	drinks/week	0.260	0.168	0.028	-0.069	0.589	1.548	0.122	
Sinadovic 2014a	drinks/week	-0.100	2.005	4.021	-4.030	3.831	-0.050	0.960	
Sinadovic 2014b	drinks/week	0.100	2.005	4.021	-3.831	4.030	0.050	0.960	
Suffoletto 2012a	drinks/drinkday	0.395	0.449	0.201	-0.484	1.274	0.881	0.378	
Suffoletto 2012b	drinks/drinkday	-0.654	0.488	0.239	-1.611	0.304	-1.338	0.181	
Sundstrom 2016a	drinks/week	0.663	0.319	0.102	0.038	1.288	2.080	0.038	
Sundstrom 2016b	drinks/week	0.840	0.324	0.105	0.205	1.474	2.593	0.010	
Wallace 2011	drinks/week	0.036	0.056	0.003	-0.074	0.146	0.641	0.521	
		0.257	0.045	0.002	0.169	0.345	5.711	0.000	

Favours Control | Favours Experimental

Fig 4. Forest plot of conventional meta-analysis. iAi, internet-based alcohol intervention.

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95% CI 49–75). No significant difference in effect size was observed between the included and non-included RCTs in the IPDMA in terms of the primary outcome (SU reduction).

There were indications of publication bias, based on a visual inspection of the funnel plot (see S1 Fig) and Egger test (intercept 1.559, $p < 0.05$), but there was no publication bias observed on the basis of Duval and Tweedie's trim-and-fill procedure (random-effects model). We could not conduct a conventional meta-analysis for our secondary outcome, as only a limited number of studies reported on it. In S3 Data, this conventional meta-analysis has been expanded with two further eligible studies published between 1 January 2017 and 30 May 2018 that could not be included in our IPDMA. Our aim here was to explore whether more recent studies could potentially alter our IPDMA results; as they did not significantly alter the effect size in our conventional analysis, we believe this confirms the robustness of our analysis.

Discussion

Principal findings and their interpretation

This study found that participants treated in iAIs showed a higher mean weekly decrease of 5.02 SUs of alcohol consumption and a greater likelihood of favourable TR (OR 2.20) than controls. Women decreased their mean weekly alcohol consumption significantly less than men (around 2 SUs). Our sensitivity analysis confirmed our assumption that this difference was not an artefact of the higher cutoff thresholds for men than for women at study inclusion (leaving women less space for alcohol reduction) [60]. More highly educated participants reduced their mean weekly consumption significantly less than lesser educated ones (around 2 SUs). This result differs from the few studies that have reported on education as a moderator of iAI treatment outcomes; these showed either improved outcomes for more educated participants [61] or no such impact [62]. For gender and education as moderators of the primary outcome, our sensitivity analyses pointed in similar directions to the outcomes of our main analysis, although the results were no longer significant. In our study, age was found to have moderated TR, with participants above 55 showing greater likelihood of post-intervention adherence to low-risk drinking recommendations than younger people. None of the other participant characteristics moderated treatment outcomes. Internet interventions appear effective when applied in community and healthcare settings, but effectiveness in work settings is still inconclusive.

Guided iAIs yielded significantly better results than unguided ones for both treatment outcomes. iAIs based solely on PNF showed a lower likelihood of TR than iAIs based on integrated therapeutic principles. Waitlist control moderated both types of treatment outcomes, with iAIs in WLC studies showing significantly better outcomes in terms of both SU reduction and TR than those in otherwise-controlled studies. It thus appears that iAI treatment outcomes could have been overestimated in studies in which WLC groups were applied as comparators. One possible explanation for such higher effect sizes in WLC studies would be that problem drinkers allocated to waiting lists might delay their alcohol reduction because they anticipate treatment soon. In contrast, people in other types of control groups might have already found alternative support by the time of the follow-up assessment, thus potentially reducing their alcohol consumption more than WLC controls. By the same token, such tendencies could deflate effect sizes in non-WLC studies [63].

The overall greater reduction of 5.02 SUs of alcohol consumption seen here in iAI treatment participants as compared with controls was higher than the 2.2 SUs we found in our earlier, conventional meta-analysis [14]. One potential explanation for that difference is the higher number of guided iAI studies included in the present IPDMA; these showed higher treatment outcomes than unguided ones. Our current finding is comparable to the 5.61-SU reduction by adult iAI participants over controls reported in the conventional meta-analysis by Kaner and colleagues [16]. Our results compare quite favourably with outcomes of patients treated in primary care settings with brief guided face-to-face interventions, who showed decreases from 2 to 4 SUs [64,65]. We were also able to assess TR in terms of NNT (4.15). Due to data limitations, conventional meta-analyses have not been able to report on NNTs or on potential moderators of iAI treatment such as gender, age, and drinking profiles [16].

Methodological considerations

To the best of our knowledge, this is the first IPDMA to test the impact of iAIs and their moderators on treatment outcomes with adequate statistical power. The included RCTs had a low overall risk of methodological bias. Our results appear robust after comparison with our two-

stage IPDMA results, as well as with those from our multiple imputation analysis and those from our conventional meta-analysis. The ANCOVA model that underlies our IPDMA implicitly relies on the MAR assumption, allowing dropout, which was 43% in our study, to depend on baseline consumption level. Although it cannot be ruled out that dropout was actually attributable to characteristics not included in the model, our MNAR sensitivity analysis suggested that the estimate of the overall effect would be reasonably stable against moderate deviations from the MAR assumption. The generalisability of our results to people in real-life settings might be hampered by poor assessment of ethnicity and by the focus on studies from high-income countries. In addition, only a small number of studies addressed effects of iAIs administered in care settings other than the community (such as in primary care practices, emergency departments, or workplaces). Another limitation is that all studies applied self-reported alcohol consumption measures, which is possibly a source of social desirability bias [66]. We also observed high heterogeneity in our analyses, and it could be explained only partly by excluding outliers or by some of the subgroup analyses that we conducted. Hence, the moderating factors we identified offer only partial clarification of moderating influences on treatment outcome. We were bound, of course, by the available data. Other moderators, such as self-efficacy or participants' preference for iAIs over other types of interventions, cannot be ruled out [67]. Longer-term outcomes of iAIs could not be assessed, as few studies addressed them.

Conclusions and clinical implications

Both men and women from different age groups and with different drinking profiles, including heavy drinking and binge-only drinking, can benefit from iAIs, and in particular from the therapeutically integrated ones as opposed to PNF-only interventions. Participants in iAIs reduced their mean alcohol consumption from 38.1 to 32.9 SUs per week, and they had a substantially higher probability of posttreatment adherence to low-risk drinking recommendations. The fact that heavy drinkers decreased their alcohol consumption by amounts similar to those of non-heavy drinkers has favourable implications, as the health impact of a given reduction is greater at higher levels of alcohol consumption [68]. Despite the finding that many participants were still consuming beyond low-risk limits at posttreatment, the population health gains could nevertheless be substantial, in view of the high number of participants that can be reached with iAIs and the positive relationship between decreased alcohol consumption and the lower risks of physical and mental health disorders in the long term. These include earlier-onset dementia [69], several types of cancer [70], cardiovascular diseases [3] (Wood 2018), and depression and anxiety [68,69,71]. iAIs have great scaling potential, partly by virtue of their swift entry procedures for patients and the relatively low cost of repeated reuse, especially if unguided. For many people, iAIs could serve as a first step towards changing their problem-drinking behaviours and towards more intensive treatment, if needed.

In view of the constraints experienced with face-to-face BAIs in primary care settings, future studies should also explore various types of brief interventions, in order to gauge how problem drinkers in such settings can best be targeted. Those could be either face-to-face BAIs or iAIs, and the latter could be guided by general practitioners (GPs) or other professionals. For some patient populations, referral to unguided forms could be more beneficial [72]. More primary care studies are needed, however, including head-to-head comparisons of unguided versus guided versus face-to-face interventions. The same applies to the optimum treatment orientations and levels of intensity and duration [73,74]. As we have seen, not all treatment participants benefited from iAIs. We therefore need to better understand for which people such interventions work, how they work, and in what contexts (an approach also highlighted

by Babor in 2008) [75,76]. A final observation is that some countries have now substantially lowered the advised limits for daily and weekly alcohol consumption, in response to mounting epidemiological evidence of health risks inherent in the conventional limits [77]. A threshold not exceeding 10 SUs of weekly alcohol consumption for both men and women has been proposed [3]. Future studies should correspondingly adjust their sample inclusion criteria based on units of alcohol consumption.

Supporting information

S1 PRISMA guidelines checklist.
(DOCX)

S1 Data. Search string.
(DOCX)

S2 Data. Request sharing variables file regarding individual RCT results. RCT, randomised controlled trial.
(DOC)

S3 Data. Results, conventional meta-analysis update (1 January 2017 and 30 May 2018).
(DOCX)

S4 Data. Data access contact list (first contact excluding coauthors).
(XLSX)

S1 Text. MNAR additional information. MNAR, missing-not-at-random.
(DOCX)

S1 Table. Risk-of-bias assessment.
(DOCX)

S2 Table. Results, primary outcome 'multiple imputation'.
(DOCX)

S3 Table. Results, secondary outcome 'multiple imputation'.
(DOCX)

S1 Fig. Publication bias funnel plot (conventional meta-analysis).
(TIF)

Acknowledgments

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