Analiza rizika od pristranosti i korištenja te procjene u analizi osjetljivosti u Cochraneovim sustavnim pregledima

Babić, Andrija

SVEUČILIŠTE U SPLITU
MEDICINSKI FAKULTET

ANDRIJA BABIĆ

ANALIZA RIZIKA OD PRISTRANOSTI I KORIŠTENJA TE PROCJENE U ANALIZI OSJETLJIVOSTI U COCHRANEOVIM SUSTAVNIM PREGLEDIMA

DOKTORSKA DISERTACIJA

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Mentorica:
prof. dr. sc. Livia Puljak, dr. med.

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1. SADRŽAJ

2. POPIS OZNAKA I KRATICA

CSP	Cochraneovi sustavni pregledi
EBM	medicina utemeljena na dokazima (engl. *evidence-based medicine*)
RoB	rizik od pristranosti (engl. *Risk of Bias*)
RCT	randomizirani kontrolirani pokus (engl. *randomized controlled trial*)
CDSR	Cochrane knjižnica (engl. *Cochrane Database of Systematic Reviews*)

3. POPIS RADOVA NA KOJIMA SE TEMELJI DOKTORSKA DISERTACIJA:

1. Assessments of attrition bias in Cochrane systematic reviews are highly inconsistent and thus hindering trial comparability. *BMC Medical Research Methodology*. 2019;9(76). https://doi.org/10.1186/s12874-019-0717-9 (2019 JIF = 3,031).
2. The judgement of biases included in the category "other bias" in Cochrane systematic reviews of interventions: a systematic survey. *BMC Medical Research Methodology*. 2019;19(1):77. doi: 10.1186/s12874-019-0718-8. (2019 JIF =3,031).
3. Overall bias methods and their use in sensitivity analysis of Cochrane reviews were not consistent. *Journal of Clinical Epidemiology*. 2020;119:57-64. doi: 10.1016/j.jclinepi.2019.11.008 (2019 JIF = 4,952).

4. UVOD

Sustavni pregledi smatraju se najvišom razinom u hijerarhiji dokaza u medicini (1). Cochraneovi sustavni pregledi (CSP) rade se prema strogim metodološkim standardima, koji se kontinuirano razvijaju i postrožuju, i zato se smatraju zlatnim standardom u sintezi dokaza (2). Cochrane je vodeća svjetska organizacija u primjeni istraživačkih metoda medicine utemeljene na dokazima (engl. *evidence-based medicine*; EBM) (3).

Važan dio metodologije sustavnih pregleda je ocjena rizika od pristranosti (engl. *Risk of Bias*; RoB) u uključenim istraživanjima (4). U kliničkim pokusima pristranost (otklon, iskrivljenje) je bilo koja sustavna pogrješka zbog koje je rezultat istraživanja različit od stvarnog. Moguća posljedica pristranosti je donošenje krivih zaključaka o učinkovitosti i sigurnosti ispitivanih intervencija (5).

U CSP-u se RoB svakog uključenog randomiziranoga kontroliranoga pokusa (engl. *randomized controlled trial*; RCT) procjenjuje rabeći alat za procjenu rizika od pristranosti, tzv. Cochraneov RoB alat (engl. *RoB tool*). Verzija tog alata objavljena 2011. godine ima sedam domena (6, 7). Novija verzija alata (RoB 2), koja je objavljena 2019. godine (8), postupno se počela rabiti u pojedinim Cochraneovim sustavnim pregledima tijekom 2020. godine (9).

U Cochraneovom RoB alatu iz 2011. godine, prva i druga domena vezane su za pristranost u biranju ispitanika (engl. *selection bias*); tu autori ocjenjuju jesu li ispitanici bili randomizirani (engl. *random sequence generation*) i kako je prikriveno tko je raspoređen u koju skupinu (engl. *allocation concealment*). Zasljepljenje ispitanika i osoblja vezano je za treći mogući rizik pristranosti (engl. *performance bias*). Zasljepljenje u procjeni ishoda, tj. analizi podataka, ako nije valjano napravljeno može voditi do četvrtog mogućeg rizika pristranosti (engl. *detection bias*).

Nepotpuno analiziranje rezultata kliničkog pokusa i sustavne razlike u skupinama vezano za broj ispitanika koji su izgubljeni iz istraživanja mogu doprinijeti petom riziku pristranosti definiranom u Cochraneovom RoB alatu (engl. *attrition bias*). Selektivno izvještavanje, tj. opisivanje samo nekih rezultata koji su u kliničkom pokusu analizirani analizira se u šestoj domeni procjene (engl. *reporting bias*). Na kraju, sedma domena procjene RoB naziva se „ostali rizici pristranosti" (engl. *other bias*), a obuhvaća sve moguće probleme i moguće rizike pristranosti koji nisu pokriveni u prvih šest domena (10).

Svaki uključeni RCT u Cochraneovom sustavnom pregledu trebao bi sadržavati RoB tablicu s dvije informacije za svaku domenu procjene – najprije se svaku od domena ocjenjuje i zatim se navodi objašnjenje te ocjene. Tri su moguće ocjene svake domene: nizak rizik, nejasan rizik ili visok rizik. Nejasan rizik označava ili nedostatak informacija za donošenje ocjene ili nemogućnost ocjene potencijalne pristranosti (10).

Za prve četiri i šestu domenu procjene RoB, Cochraneov priručnik za izradu sustavnih pregleda (engl. *Cochrane handbook for systematic reviews of interventions*) davao je precizne upute i primjere koji autorima pomažu u ocjenjivanju tih domena (10). Kada je u pitanju rizik od pristranosti zbog gubitka ispitanika (engl. *attrition bias*), Cochraneov priručnik davao je nejasne upute za procjene te vrste pristranosti, što može uzrokovati razlike u definiranju te vrste pristranosti u Cochraneovim sustavnim pregledima (11, 12).

Kada je u pitanju sedma domena, ostali mogući uzroci pristranosti (engl. *other bias*), Cochraneov priručnik također je davao nejasne upute (10). Jasnije upute i navođenje primjera takvih izvora pristranosti pomogli bi da autori sustavnih pregleda mogu prepoznati ostale vrste pristranosti kada se sretnu s takvom situacijom u primarnim istraživanjima uključenim u sustavne preglede (11).

Važnost jasnih uputa i primjera za procjenu svih domena rizika od pristranosti važna je i zbog procjene ukupnog rizika pristranosti na razini istraživanja (engl. *overall bias*) koji se često u sustavnim pregledima rabi za podjelu uključenih istraživanja na one koje su pouzdane (nizak rizik od pristranosti) i one koje su manje pouzdane (visok ili nejasan rizik od pristranosti) te se temeljem te procjene mogu raditi analize osjetljivosti u kojima se pojedina istraživanja isključuju iz meta-analize zbog potencijalno nepouzdanih rezultata (13).

Procjena ukupnog rizika pristranosti može se provesti na više razina, a jedna od njih je „Zbrajanje rizika pristranosti za pregled kao cjelinu (na razini svih istraživanja ili na razini svih ishoda)". Cochraneov priručnik navodi: „Zbrajanje ukupnog rizika pristranosti u pregledu trebalo bi izbjegavati iz dva razloga (10). Prvo, to zahtijeva vrijednosne procjene, a za donošenje odluke su ishodi ključni. Često ne postoje podaci iz istraživanja uključenih u pregled za neke ishode koji mogu biti ključni (14-16), poput neželjenih učinaka [nuspojava (17)], a rizik pristranosti je rijetko isti za sve ishode koji su ključni za takvu procjenu. Drugo, procjene o tome koji su ishodi ključni za odluku mogu se razlikovati, zbog razlika kako u društvenim vrijednostima tako i drugim čimbenicima, poput osnovnog rizika. Procjene o ukupnom riziku pristranosti dokaza kroz istraživanja i ishode trebalo bi donositi u određenom kontekstu, primjerice u kontekstu smjernica za kliničku praksu, a ne u kontekstu sustavnih pregleda kojima je svrha donošenje odluka u različitim okruženjima (18)."

Čitanjem velikog broja CSP-ova moguće je uočiti kako autori na različite načine procjenjuju rizik povezan s pojedinim opisima moguće pristranosti povezane s gubitkom ispitanika i ostalih mogućih izvora pristranosti. Također je moguće uočiti da ima CSP-ova koji određuju ukupan rizik od pristranosti te na temelju procjene rizika od pristranosti rade analize osjetljivosti (engl.

sensitivity analysis) i selektivno uključuju rezultate pojedinih istraživanja u meta-analize. Niska pouzdanost procjena i razlike među pojedinim procjeniteljima već su opisani u literaturi (19-21).

5. PREGLED METODOLOGIJE OBJEDINJENIH RADOVA

5.1 Prvo istraživanje: Analiza procjene rizika od pristranosti od gubitka ispitanika

Proveli smo sustavnu analizu objavljenih Cochraneovih sustavnih pregleda. Pretražili smo Cochraneovu knjižnicu i izdvojili CSP-ove o intervencijama objavljene od srpnja 2015. do lipnja 2016. koji su uključili RCT-ove. Dva su autora neovisno analizirala sve naslove/sažetke kako bi provjerili zadovoljavaju li uvjete uključenja. Planirali smo, ako bude potrebno, neslaganja u procjeni riješiti uključivanjem trećeg autora, no to nije bilo potrebno. Jedan je autor izvadio podatke samostalno, a drugi je nasumično provjerio 10% podataka. Isključili smo dijagnostičke CSP, prazne CSP, preglede sustavnih pregleda (engl. *overviews of systematic reviews*) i povučene CSP. Izvadili smo sljedeće podatke: naslov CSP-a, prezime prvog autora, datum objave (mjesec, godina), broj istraživanja uključenih u CSP, procjena rizika od pristranosti zbog gubitka ispitanika za svako uključeno istraživanje (nizak, nejasan ili visok rizik), razlozi za određenu ocjenu (popratni komentari) navedeni u RoB tablici za svako uključeno istraživanje, postojanje razlike između različitih CSP-ova, kao i unutar istog. Ako su postojali, izvadili smo i preciznu definiciju za pristranost zbog gubitka ispitanika u Metodama, statističku metodu definiranu kao odgovarajuća/neodgovarajuća vezano za pristranost zbog gubitka ispitanika te definiciju pristranosti zbog gubitka ispitanika u Rezultatima. Napravili smo deskriptivnu statistiku (frekvencije i postotci).

5.2 Drugo istraživanje: Analiza procjene rizika od ostalih mogućih izvora pristranosti

Proveli smo sustavnu analizu objavljenih Cochraneovih sustavnih pregleda. Pretražili smo Cochraneovu knjižnicu i izdvojili CSP-ove o intervencijama objavljene od srpnja 2015. do lipnja 2016. koji su uključili RCT-ove. Dva su autora neovisno analizirala sve naslove/sažetke kako bi provjerili zadovoljavaju li uvjete uključenja. Planirali smo, ako bude potrebno, neslaganja u procjeni riješiti uključivanjem trećeg autora, no to nije bilo potrebno. Jedan je autor izvadio podatke samostalno, a drugi je nasumično provjerio 10% podataka. Isključili smo dijagnostičke CSP, prazne CSP, preglede sustavnih pregleda (engl. *overviews of systematic reviews*) i povučene CSP. Izvadili smo sljedeće podatke: naslov CSP-a, prezime prvog autora, datum objave (mjesec, godina), broj istraživanja uključenih u CSP, postojanje domene za ostale rizike od pristranosti u RoB tablicama, procjena ostalih rizika od pristranosti svih uključenih istraživanja u svakom analiziranom CSP-u (nizak, nejasan ili visok rizik), razlozi za određenu procjenu ostalih rizika od pristranosti navedeni u RoB tablici (popratni komentari), postojanje razlike između različitih CSP-ova, kao i unutar istog. Napravili smo deskriptivnu statistiku (frekvencije i postotci).

5.3 Treće istraživanje: Analiza procjene ukupnog rizika od pristranosti na razini ishoda ili istraživanja te korištenja te procjene u analizi osjetljivosti

Proveli smo sustavnu analizu objavljenih Cochraneovih sustavnih pregleda. Pretražili smo Cochraneovu knjižnicu i izdvojili CSP-ove o intervencijama objavljene od srpnja 2015. do lipnja 2018. koji su uključili RCT-ove. Dva su autora neovisno analizirala sve naslove/sažetke kako bi provjerili zadovoljavaju li uvjete uključenja. Planirali smo, ako bude potrebno, neslaganja u procjeni riješiti uključivanjem trećeg autora, no to nije bilo potrebno. Jedan je autor izvadio

podatke samostalno, a drugi je provjerio sve povađene podatke. Isključili smo dijagnostičke CSP, prazne CSP, preglede sustavnih pregleda (engl. *overviews of systematic reviews*) i povučene CSP. Izvadili smo sljedeće podatke: naslov CSP-a, prezime prvog autora, datum objave (mjesec, godina) i broj istraživanja uključenih u CSP. Ako su postojali, izvadili smo i preciznu definiciju ukupnog rizika od pristranosti u Metodama, navođenje da su istraživanja isključena ili nisu isključena zbog rizika od pristranosti, navode o planiranju analize osjetljivosti na osnovi rizika pristranosti te podatke o provedbi takve vrste analize osjetljivosti za kvalitetu u Rezultatima. Napravili smo deskriptivnu statistiku (frekvencije i postotci).

6. SAŽETI PREGLED REZULTATA OBJEDINJENIH RADOVA

6.1 Prvo istraživanje: Analiza procjene rizika od pristranosti od gubitka ispitanika

U prvom su istraživanju analizirane ukupno 10292 ocjene (nizak rizik, nejasan rizik ili visok rizik) pristranosti zbog gubitka ispitanika (engl. *attrition bias*) i pripadajućih objašnjenja koja potkrepljuju ocjenu (engl. *supporting explanation*) iz 729 CSP-ova. Kategorizirali smo ocjene i pripadajuća objašnjenja u četiri kategorije i utvrdili da je većina tih objašnjenja bila nejasna. Postotak ispitanika koji su otpali iz istraživanja, kao i statistika korištena za iste, ocjenjivane su veoma različito. Isti postotak otpalih ispitanika i ista statistika koja je korištena za njihove podatke u različitim su CSP-ovima različito ocjenjivani. U jednoj trećini analiziranih CSP-ova autori su dali više od jedne kategorije pripadajućih objašnjenja, a neki su dali do četiri različite kategorije istih. Nedosljednosti su pronađene u broju ocjena za rizik od gubitka ispitanika (više ocjena za isto istraživanje), nazivu domene rizika od pristranosti (nisu je svi autori nazvali „*attrition bias*“) i ocjenjivanju identičnog pripadajućeg objašnjenja u istom CSP-u (identično objašnjenje različito ocijenjeno u istom CSP-u).

6.2 Drugo istraživanje: Analiza procjene rizika od ostalih mogućih izvora pristranosti

U drugom je istraživanju analizirano ukupno 768 CSP-ova koji su uključili 11369 randomiziranih kontroliranih pokusa (RCT). Pronađena su 602 (78%) CSP-a koja su imala domenu ostalih mogućih izvora pristranosti (engl. *other bias*) u RoB alatu i uključivala su ukupno 7811 RCT-ova. U tablici rizika od pristranosti, koja se treba nalaziti u svakom CSP-u, za 337 CSP-ova za barem jedan od uključenih RCT-ova navedeno je da nije pronađen ostali mogući izvor pristranosti, no

pripadajuća objašnjenja nedosljedno su ocijenjena kao nizak, nejasan ili visok rizik od pristranosti. U 524 CSP-a koja su opisala različite ostale rizike od pristranosti, bilo je 5762 pojedinačna tipa pripadajućih objašnjenja koja smo kategorizirali u 31 skupinu. Ocjene potpuno istih objašnjenja su bile veoma nedosljedne. Nadalje, pronašli smo brojne druge nedosljednosti u izvješćivanju o ostalim rizicima od pristranosti u CSP-ovima.

6.3 Treće istraživanje: Analiza procjene ukupnog rizika od pristranosti na razini ishoda ili istraživanja te korištenja te procjene u analizi osjetljivosti

Rezultati trećeg istraživanja pokazali su da od 1452 analizirana CSP-a, 409 (28%) spominje procjenu ukupnog rizika od pristranosti (engl. *overall RoB*) na razini istraživanja ili ishoda. U 107 (26%) od tih 409 CSP-ova autori jasno navode ključne domene koje određuju ukupni RoB, dok u preostalima metode procjene ukupnog rizika od pristranost nisu bile u skladu s Cochraneovim priručnikom. Među 268 CSP-ova koji su napravili analizu osjetljivosti temeljenu na ukupnom riziku od pristranosti, u 56 (21%) su autori izvijestili o statistički značajnoj razlici u rezultatima za barem jedan ishod u odnosu na početnu analizu.

7. DISKUSIJA

U okviru ove doktorske disertacije objavljena su tri znanstvena rada o različitim domenama procjene rizika od pristranosti u Cochraneovim sustavnim pregledima za koje smo smatrali da ih autori nedosljedno rabe. Analizirali smo veliki broj CSP-ova te pronašli nedosljednosti u procjeni rizika od pristranosti zbog gubitka ispitanika i ostalih rizika od pristranosti. U trećem radu smo istraživali rade li autori CSP-ova procjenu ukupnog rizika od pristranosti te na osnovi nje i analizu osjetljivosti i došli do rezultata da oko četvrtina autora CSP-ova rade takvu procjenu iako to nije u skladu s Cochraneovim priručnikom prema kojem bi se autori trebali ravnati. Cochraneovi autori nemaju jedinstven pristup procjeni rizika od pristranosti ni za jednu domenu koju smo istraživali.

Istražujući domenu procjene rizika od pristranosti zbog gubitka ispitanika nismo primijetili jasna brojčana pravila o postotku gubitka ispitanika u skupinama ili jasna pravila o statističkim metodama koje su korištene, a koje su dosljedno označavane kao nizak, nejasan ili visok rizik od pristranosti. Također, jedna je trećina autora CSP-ova imala više od jedne kategorije objašnjenja za domenu gubitka ispitanika, a neki su imali čak do četiri različite kategorije. U istom radu su pronađene nedosljednosti čak i s brojem ocjena, imenima domene kao i različitim ocjenama za identična objašnjenja u istom CSP-u.

U Cochraneovom priručniku piše: „*Podaci o ishodima koji nedostaju zbog odustajanja tijekom istraživanja ili isključenja iz analize povećavaju mogućnost da je promatrana procjena učinka pristrana*“. Izraz pristranosti zbog gubitka ispitanika rabi se i za isključivanje nekih podataka iz analize i za odustajanje nekih ispitanika (10). U kontekstu ove domene rizika od pristranosti često se spominju različite statističke metode za unošenje podataka koji nedostaju. Na primjer, autori istraživanja mogu rabiti ITT analizu ili „modificiranu ITT analizu“. Pojam "ITT analiza", kao i onaj modificirana, nema uvijek jasnu i dosljednu definiciju te se ne rabi dosljedno u izvještajima

o istraživanjima (22). Zbog toga Cochraneov priručnik preporučuje da autori sustavnih pregleda uvijek traže informacije o tome tko je točno uključen u takvu analizu (10). Pronašli smo i da su jednostavne imputacije poput korištenja zadnjih izmjerenih parametara (engl. *last observation carried forward*; LOCF) i dalje vrlo popularne unatoč upozorenjima statističara protiv njihove upotrebe (23).

Iako je bilo teško usporediti ocjenjivanje različitih statističkih metoda zbog više kategorija objašnjenja ipak smo pronašli vrlo nedosljedne ocjene za različite statističke metode. Čak i u CSP-ovima u kojima je jedino dostupno objašnjenje bilo statističko, nismo mogli doći do općeg zaključka jer je većina autora ocjenjivala prisutnost ITT analize kao nizak rizik od pristranosti, no i u pregledima koji su izričito izvijestili da nije bilo ITT analize, taj se nedostatak također pretežno ocjenjivao kao nizak rizik od pristranosti.

Ranije je objavljeno da gubitak ispitanika manji od 5% neće dovesti do pristranosti, dok stope gubitka iznad 20% dovode u pitanje valjanost istraživanja (24). Cochraneov priručnik ne daje jasne smjernice o ukupnom gubitku ispitanika ili gubitku po skupini koje bi predstavljale rizik od pristranosti.

U našem prvom istraživanju smo otkrili da su brojčani pokazatelji onoga što predstavlja gubitak ispitanika bili u velikoj mjeri nedosljedni. Kada smo kategorizirali prijavljeni postotak gubitka ispitanika u skupini s većim gubitkom, gubitak u skupini manji od 10% ocjenjivan je kao nizak rizik od pristranosti u 83% slučajeva, gubitak od 10-20% je ocjenjivan kao nizak rizik od pristranosti u 64% slučajeva, dok je gubitak od 20-30% ocjenjivan kao nizak rizik od pristranosti u 57% slučajeva. Ako pogledamo većinsko mišljenje Cochraneovih autora, prag od iznad 30% se uglavnom smatra visokim rizikom od pristranosti jer je 61% ocjena tako naznačilo u CSP-ima gdje se jedini komentar autora odnosio na udio izgubljenih ispitanika.

Samo korištenje rizika od pristranosti kao alata ima nisku podudarnost između različitih procjenitelja (25). Tvrdi se da to može imati negativne učinke na donošenje odluka i kvalitetu zdravstvene zaštite (26). U istraživanju koje su proveli da Costa i suradnici pokazalo se da standardizirana intenzivna edukacija o procjeni RoB-a može značajno poboljšati pouzdanost procjena učinjenih s pomoću Cochraneovog RoB alata (27). Naše prvo istraživanje pokazuje da bismo prvo trebali imati standardizirane upute o tome koje situacije stvarno predstavljaju rizik od pristranosti zbog gubitka ispitanika. S jasnim uputama bilo bi mnogo lakše postići veću podudarnost procjene RoB-a, čak i bez službene edukacije. One bi trebale jasno odrediti što autori sustavnih pregleda trebaju procijeniti, poput četiri kategorije koje smo mi rabili u našem istraživanju, uključujući postotak gubitka ispitanika po skupini i razliku između skupina, jesu li prijavljeni razlozi za gubitak ispitanika te koja je odgovarajuća statistička metoda korištena za rješavanje problema s gubitkom ispitanika. Bez uputa autori se mogu ponašati onako kako smo mi utvrdili u našim rezultatima – mogu upotrijebiti jednu ili više od tih kategorija kako već oni osobno smatraju prikladnim.

Nedovoljno i nejasno izvještavanje o domeni „ostalih izvora pristranosti“ bilo je vrlo često u Cochraneovim pregledima koje smo analizirali. Najčešća objašnjenja koja smo pronašli bila su "nije opisano / nejasno", što je osobito zagonetno jer ta domena nije specifična kao ostalih šest domena RoB alata, pa je stoga teško shvatiti što znači da druga pristranost nije opisana ili da je nejasna. Ako autori nisu pronašli druge izvore pristranosti ili ako su mislili da ih ne mogu procijeniti zbog kratkoće izvještaja ili jezičnih problema, trebali su to navesti. Za neka je istraživanja jedino objašnjenje bilo da su ostali izvori pristranosti bili "prikladni". Bez ikakvih daljnjih objašnjenja, čitatelji ne mogu znati što su točno Cochraneovi autori smatrali prikladnim u pogledu ostalih mogućih izvora pristranosti. Mnogi analizirani sustavni pregledi imali su veliki

broj uključenih istraživanja, pa su se stoga neki komentari ponavljali više puta u istom sustavnom pregledu.

Najčešće korištena kategorija ostalih izvora pristranosti odnosila se na osnovne karakteristike ispitanika. U RCT-ovima bi randomizacija trebala osigurati raspodjelu ispitanika u skupine koje se razlikuju samo po intervenciji koju su primili. Takvom bi se raspodjelom karakteristike sudionika koje mogu utjecati na ishod trebale raspodijeliti na jednake dijelove po ispitivanim skupinama, tako da se može pretpostaviti da su bilo kakve razlike u ishodima posljedica intervencije (28). Neravnoteža osnovnih obilježja među skupinama može ukazivati da je nešto s postupkom randomizacije pogrješno ili da su oni možda i slučajni (29). Velike neravnoteže se mogu dogoditi zbog namjernih postupaka ispitivača kojima je cilj namjerno ugroziti postupak randomizacije (30) ili zbog nenamjernih pogrješaka.

Lundh i suradnici su 2017. godine objavili Cochraneov sustavni pregled o financiranju industrije i ishodima istraživanja u koji su uključili 75 primarnih istraživanja. Rezultati pokazuju da komercijalno financiranje dovodi do povoljnijih rezultata i zaključaka o učinkovitosti u odnosu na neprofitno financiranje. Zaključili su da komercijalni izvor financiranja dovodi do rizika od pristranosti koji se ne može objasniti standardnim domenama Cochraneove RoB procjene (31). Rasprava o tome predstavlja li financiranje izvor pristranosti ili ne još traje unutar Cochranea, s tim da neki smatraju da je komercijalno financiranje jasan rizik od pristranosti, dok drugi tvrde suprotno (32, 33). Ta rasprava očito odražava trenutnu situaciju u kojoj mnogi autori CSP-ova i dalje rabe financiranje i sukob interesa kao izvor pristranosti unutar domene ostalih izvora pristranosti, unatoč službenom upozorenju protiv toga iz Cochraneovog priručnika, kao što smo pokazali u našem drugom istraživanju. U njemu smo pokazali i da autori analiziranih CSP-ova u velikoj mjeri rabe dostupnu opciju za prilagodbu RoB tablice. Ukupno 102 (13%) od 768

analiziranih CSP-ova nisu uopće rabile domenu ostalih izvora pristranosti u RoB tablici; ta domena bila je iz njihovih tablica izbrisana. Autori moraju namjerno ukloniti ili dodati neke domene ako žele prilagoditi zadane postavke RoB tablice koja standardno ima sedam domena. Među 102 CSP-a koji nisu imali ovu domenu, 33% je imalo komentare o drugim potencijalnim izvorima pristranosti u ostalim dijelovima rada. Nejasno je zašto neki autori rabe samo tekst za komentare o drugim pristranostima, umjesto da u tu svrhu rabe RoB tablicu. Osim toga smo primijetili da je u mnogim CSP-ova osim ove, bilo i drugih prilagodbi RoB tablice, koje su imale od jedne do šest drugih, standardnih RoB domena. Točno polovica onih CSP-ova bez domene ostalih izvora pristranosti je u RoB tablici imala manje od šest ostalih standardnih domena. Većina Cochraneovih autora je odlučila upotrijebiti ovu domenu kako bi opisali potencijalne dodatne pristranosti koje nisu pokrivene u prvih šest domena alata RoB.

U našem trećem istraživanju smo došli do rezultata da je mali broj Cochraneovih autora spomenuo procjenu ukupnog rizika od pristranosti, a još manje njih je takvu procjenu i opisalo. Njihova procjena u većini analiziranih slučajeva nije bila u skladu s Cochraneovim priručnikom. Prema Cochraneovom priručniku (10), autori CSP-ova bi trebali izbjegavati ocjenjivanje ukupnog RoB-a. Unatoč toj preporuci, otkrili smo da je četvrtina analiziranih CSP-ova spomenula procjenu ukupnog RoB-a na razini pojedinog istraživanja. Naši su rezultati u skladu s prethodnim istraživanjima koja su izvijestila da autori ponekad procjenjuju ukupni RoB te rade analizu osjetljivosti na temelju takve procjene (18).

Iako se u samo u četvrtini CSP-ova spominjala procjena ukupnog RoB-a, u više od trećine njih autori su jednostavno naznačili da je rizik od pristranosti na razini pojedinog istraživanja procijenjen na temelju kriterija iz Cochraneova priručnika, bez navođenja tih kriterija. Nadalje,

niti jedan od tih CSP-ova nije izvijestio da su stvarno uradili ukupnu procjenu RoB-a na razini istraživanja, a jedini spomen takve procjene nalazio se u odjeljku Metode.

Cochraneov priručnik ne savjetuje ocjenjivanje ukupnog rizika pristranosti, a autori se pozivaju na definiciju iz priručnika, koju nemaju, te u konačnici nisu izvijestili podatke o takvoj procjeni. Stoga nije jasno zašto gotovo deset posto analiziranih CSP-ova uopće u odjeljku o metodama sadrži takav tekst.

Samo četvrtina CSP-ova koji su spominjali procjenu ukupnog rizika pristranosti učinila je to u skladu s Cochraneovim priručnikom u kojem piše da će ukupna procjena RoB-a ovisiti o ključnim domenama te su naveli koje domene smatraju ključnima.

Neki od njih su spomenuli ključne domene bez da su ih definirali, što dovodi do sumnje da neki autori jednostavno kopiraju i zalijepe tekst o ukupnom RoB-u iz drugih CSP-ova bez stvarne namjere procjene istog, a Cochraneove uredničke skupine očito ne vode dovoljno računa o ispravnosti takve procjene.

S druge pak strane, postoji jedan primjer poput CSP-a koje su proveli Heal i suradnici (34), koji su očito svjesni mogućih problema s procjenom ukupnog rizika pristranosti te su jasno napisali: "*Znamo da ne postoji prihvaćena definicija što predstavlja istraživanje s visokim rizikom od pristranosti*", a nakon toga su definirali koje ključne domene određuju ukupni RoB u istraživanjima uključenima u njihov CSP.

U više se istraživanja pokazalo da je metodologija CSP-ova bolja u odnosu na ne-Cochraneove sustavne preglede (35, 36). Cochraneov RoB alat prihvaćen je i izvan Cochranea; rabio se u 100% CSP-ova i u 31% ne Cochraneovih sustavnih pregleda objavljenih do kraja 2014. godine, ali vrlo često taj alat nije korišten na odgovarajući način (18). Više istraživanja je pokazalo da je u CSP-

ovima velika učestalost nedosljednosti povezanih s procjenom RoB-a (37-40) te naša istraživanja dodatno potvrđuju prethodne rezultate.

Pronašli smo krajnje nedosljedan pristup procjeni ukupnog RoB-a na razini istraživanja u CSP-ovima od kojih su mnogi u suprotnosti sa savjetima iz Cochraneovog priručnika. Već je objavljeno da pojednostavljeni pristup procjeni ukupnog RoB-a, kao što je jednako tretiranje svih domena ili podrazumijevanje da pojedinačna domena s visokim RoB-om ukazuje na to da cijelo istraživanje ima visok RoB, nije dobar (41).

U trećem smo istraživanju također utvrdili da većina analiziranih CSP-ova planira uraditi analizu osjetljivosti kako bi se istražio učinak RoB-a, tj. kvalitete uključenih ispitivanja, na rezultate. To je u također u skladu s prethodnim rezultatima (18). Međutim, samo je petina tih sustavnih pregleda izvijestila da je stvarno i napravila takvu analizu, što je u skladu s rezultatima Jørgensena i suradnika (18). Mnogi analizirani CSP-ovi u našem uzorku izvijestili su da nisu mogli provesti analizu osjetljivosti jer je bilo samo nekoliko "visokokvalitetnih" istraživanja s niskim rizikom od pristranosti.

Često nam nije bilo jasno jesu li autori stvarno planirali analizu osjetljivosti temeljenu na RoB-u, jer su spomenuli samo "kvalitetu istraživanja", a tada čitatelj ne može biti siguran odnosi li se to na RoB ili bilo koju drugu mjeru kvalitete istraživanja. Također su i pristupi izrade analiza osjetljivosti temeljenih na RoB-u bili vrlo raznoliki. Jedan od posebnih razloga za zabrinutost uključuje izrazito heterogene pristupe u određivanju brojčanih pokazatelja stope gubitka ispitanika koji su povezani s određenom ocjenom RoB-a što smo naglasili u prvom istraživanju. Nejasne upute iz Cochraneova priručnika u vezi s procjenom te vrste pristranosti mogu pridonijeti ovoj uočenoj heterogenosti (10).

U naša istraživanja nismo uključili sustavne preglede koji nisu Cochraneovi jer ti pregledi, za razliku od CSP-ova, nemaju obvezu rabiti Cochraneovu metodologiju. CSP-ove izrađuje jedna organizacija koja bi usprkos velikom broju uredničkih skupina za različita područja, ipak trebala voditi računa o dosljednosti metodologije.

Naša istraživanja imaju i svoja ograničenja. Kao prvo, korišten je prigodni uzorak ograničenog broja CSP-ova objavljenih u roku od jedne do tri godine jer su nas zanimali nedavno objavljeni CSP-ovi. Nadalje, analizirali smo samo CSP-ove, a ne i njihove protokole. Neke informacije koje smo tražili u CSP-ovima bi se možda mogle naći u njihovim protokolima. Ali ako su Cochraneovi autori naknadno odlučili promijeniti neke aspekte svoje metodologije ili ako nisu mogli primijeniti određene metodološke pristupe koje su planirali, o svemu bi tome trebali izvijestiti u CSP-u. Moguće je da su počinjene neke nenamjerne pogrješke u kategorizacijama, pa smo zbog transparentnosti odlučili objaviti sve kategorije i potkategorije objašnjenja na koje smo naišli u dopunskom materijalu naših radova.

Cochrane je razvio revidirani Cochraneov alat za procjenu rizik od pristranosti u randomiziranim istraživanjima (RoB 2) (8). Taj se alat razlikuje od starog. Domena procjene RoB-a zbog gubitka ispitanika koja se na engleskom jeziku zove *attrition bias* se sada drukčije zove, domene ostalih izvora pristranosti (engl. *other bias*) više nema, a službena ukupna procjena RoB-a (engl. *overall bias*) je sada obvezna i određuje se s pomoću računalnog programa nakon što se ocijene ostale domene. Struktura domena je nešto drugačija i postoje signalna pitanja s pet odgovora. Na temelju tih odgovora, računalni algoritam dodijeli RoB ocjenu svakoj domeni, a na kraju odredi i ukupni RoB. Novi alat objavljen je u časopisu BMJ u kolovozu 2019. i u vrijeme pisanja ove disertacije uporaba RoB 2 još nije bila obavezna u svim CSP-ovima koji su u izradi. Ostaje nam vidjeti kako će se rabiti, kako će se autori educirati za prelazak na novi alat i što će Cochrane učiniti da se novi

alat rabi dosljedno. Budući da je RoB 2 alat mnogo složeniji u usporedbi s RoB alatom iz 2011. godine, analiziranom u ovoj disertaciji, upitno je hoće li ga široko usvojiti autori ne-Cochraneovih sustavnih pregleda.

Rezultati ova tri istraživanja imaju vrlo relevantna praktična značenja. CSP-ovi donose zaključke za kliničku praksu i buduća istraživanja. Nepoželjna je praksa ako CSP-ovi sadrže nedosljedne rezultate o procjeni rizika od pristranosti, a osobito ako se ta procjena na nedosljedan način rabi za uključivanje rezultata u meta-analize i analize osjetljivosti. U tom slučaju je nužno poboljšati upute za Cochrane autore da bi se dokazi iz uključenih istraživanja dosljedno procjenjivali te donosile dosljedne preporuke za praksu i buduća istraživanja. U tom je svjetlu pozitivan pomak nagrada Bill Silverman koju je Cochrane dodijelio mentorici ove disertacije prof. dr. sc. Liviji Puljak na godišnjoj generalnoj skupštini organizacije održanoj 16. prosinca 2020. godine. Ta se nagrada dodjeljuje svake godine jednoj osobi i izričito priznaje Cochraneovu vrijednost kritike s ciljem poboljšanja rada organizacije Cochrane te postizanja Cochraneovog cilja da pomogne zdravstvenim djelatnicima, pacijentima i ostalim korisnicima u donošenju dobro informiranih odluka o zdravstvenoj zaštiti pružajući najbolje moguće dokaze o učincima zdravstvenih intervencija. Ta je nagrada dodijeljena upravo za znanstveni rad objavljen u časopisu Journal of Clinical Epidemiology (38) u kojemu je ukazano na grješke i nedosljednosti koje autori Cochraneovih sustavnih pregleda rade prilikom procjenjivanja rizika od pristranosti u uključenim radovima.

8. ZAKLJUČAK

Važan dio metodologije Cochraneovih sustavnih pregleda je procjena rizika od pristranosti. U sklopu ove disertacije u tri istraživanja analizirane su tri domene procjene RoB-a i utvrđene su nedosljednosti u metodama procjene rizika od pristranosti zbog gubitka ispitanika, ostalih izvora od pristranosti te ukupnog rizika od pristranosti.

U prvom je istraživanju utvrđeno da autori CSP-ova rabe različite kategorije objašnjenja kojima potkrepljuju ocjene te ih imaju od jedne do četiri. Također, autori rabe različite brojčane pokazatelje stope gubitka ispitanika za donošenje istih procjena rizika, različito nazivaju ovu domenu te unutar istog CSP-a daju različite ocjene za potpuno ista objašnjenja.

U drugom istraživanju je utvrđeno da Cochraneovi autori koji imaju ovu domenu spominju širok raspon ostalih izvora pristranosti u RoB alatu te također daju različite ocjene za potpuno ista objašnjenja. U nizu CSP-ova RoB tablica je promijenjena na način da su izbrisane standardne domene, a unutar domene ostalih izvora pristranosti navode se informacije za koje Cochraneov priručnik izričito navodi da se u toj domeni ne bi trebale spominjati.

U trećem istraživanju utvrđeno je da manjina Cochraneovih autora spominje procjenu ukupnog rizika od pristranosti te da samo četvrtina njih to čini u skladu s preporukama iz Cochraneova priručnika. Većina analiziranih CSP-ova u metodama je navela kako će uraditi analizu osjetljivosti kako bi se istražio učinak RoB-a ili kvalitete uključenih istraživanja na rezultate, ali samo je petina tih pregleda izvijestila da su takvu analizu napravili, najčešće zato što je bilo dostupno samo nekoliko visokokvalitetnih istraživanja s niskim RoB-om.

Autorima Cochraneovih sustavnih pregleda trebaju jasne smjernice o procjeni različitih domena RoB-a jer nedosljednost u procjeni umanjuje pouzdanost i usporedivost CSP-ova. To bi pomoglo

u lakšem donošenju kako odluka o riziku od pristranosti tako i donošenju pouzdanih odluka u zdravstvu.

9. SAŽETAK

Uvod: Važan dio metodologije sustavnog pregleda je procjena rizika od pristranosti (engl. *risk of bias*; RoB) u uključenim istraživanjima. Cochraneovi sustavni pregledi (CSP) smatraju se zlatnim standardom u pogledu metodologije sustavnog pregleda, ali Cochraneove upute za procjenu nekih domena rizika od pristranosti nejasne su, što može dovesti do nedosljednosti u procjenama autora. Cilj ove doktorske disertacije je bio kroz provedbu tri istraživanja analizirati dosljednost ocjena i pripadajućih objašnjenja za domene gubitka ispitanika (engl. *attrition bias*) te ostalih izvora od pristranosti (engl. *other bias*), kao i rabe li autori CSP-ova procjenu ukupnog rizika od pristranosti (engl. *overall bias*) te na osnovi nje i analizu osjetljivosti (engl. *sensitivity analysis*) u sustavnim pregledima o intervencijama objavljenima u Cochraneovoj bazi podataka sustavnih pregleda.

Metode: Analizirani su svi CSP-ovi o intervencijama objavljeni od srpnja 2015. do lipnja 2016. godine koji su uključili randomizirane kontrolirane pokuse, a u trećem istraživanju CSP-ovi objavljeni od srpnja 2015. do lipnja 2018. godine. Izvađeni su podatci o broju uključenih istraživanja, ocjenama za domene gubitka ispitanika i ostalih izvora pristranosti (nizak, nejasan ili visok) te pripadajuća objašnjenja. Ocijenjeno je koliko CSP-ova ima različite ocjene za isto pripadajuće objašnjenje. Analizirani su podatci o metodama procjene ukupnog rizika od pristranosti za cijelo istraživanje kao i detalji o metodama koje se rabe za izradu analiza osjetljivosti na temelju RoB-a. Korištena je deskriptivna statistika.

Rezultati: *Prvo istraživanje:* U glavnu analizu uključene su 10292 ocjene i pripadajuća objašnjenja za pristranost zbog gubitka ispitanika iz 729 CSP-ova. Pripadajuća objašnjenja za te ocjene razvrstane su u četiri kategorije i utvrđeno je da je većina objašnjenja bila nejasna. Brojčani pokazatelji postotka gubitka ispitanika kao i korištene statističke metode su ocjenjivane vrlo različito. Jedna trećina autora CSP-ova je imala više od jedne kategorije pripadajućih objašnjenja;

neki su imali do četiri različite kategorije. Pronađene su nedosljednosti čak i s brojem ocjena, imenima ove domene i različitim ocjenama za ista pripadajuća objašnjenja u istom CSP-u. *Drugo istraživanje:* Analizirano je 768 CSP-ova koji su uključivali 11369 randomiziranih kontroliranih pokusa (RCT). Bilo je 602 (78%) CSP-a koji su imali domenu „ostalih izvora pristranosti" u RoB alatu, a uključivale su ukupno 7811 RCT-ova. U RoB tablici 337 CSP-ova za barem jedno od uključenih istraživanja je naznačeno da nije pronađen nijedan ostali izvor pristranosti, a pripadajuća objašnjenja su nedosljedno ocijenjena kao nizak, nejasan ili visok izvor pristranosti. U 524 CSP-a koji su opisivali razne ostale izvore pristranosti je bilo 5762 pojedinačna tipa objašnjenja koje su razvrstana u 31 skupinu. Ocjene istih pripadajućih objašnjenja bile su vrlo nedosljedne. Pronađene su brojne druge nedosljednosti u izvještavanju o ostalim izvorima pristranosti u CSP-ima. *Treće istraživanje:* Od 1452 analizirana CSP-a, 409 je spomenulo procjenu ukupnog RoB-a na razini istraživanja. U 107 CSP-ova su autori jasno odredili ključne domene koje određuju ukupni RoB, dok u preostalim CSP-ovima procjena ukupnog rizika od pristranosti nije bila u skladu s Cochraneovim priručnikom. Među 268 CSP-ova koji su imali bilo kakvu analizu osjetljivosti povezanu s RoB-om, u 56 (21%) pregleda su autori izvijestili o značajnoj promjeni rezultata za barem jedan ishod u odnosu na početnu analizu.

Zaključak: U analiziranim CSP-ovima pronađena je velika nedosljednost u metodama procjene rizika od pristranosti zbog gubitka ispitanika kao i ostalim izvorima pristranosti. Vrlo heterogeni pristupi procjeni ukupnog RoB-a na razini primarnog istraživanja i upotreba RoB-a za analize osjetljivosti mogu dati nedosljedne i neusporedive rezultate u Cochraneovim pregledima. Autorima sustavnih pregleda trebaju jasne smjernice o procjeni različitih domena RoB-a. Jasne upute o procjeni RoB-a će poboljšati pouzdanost Cochraneova alata za procjenu rizika od

pristranosti, pomoći autorima u donošenju odluka o riziku od pristranosti i u donošenju pouzdanih odluka u zdravstvu.

10. SUMMARY

Background: An essential part of the systematic review methodology is the appraisal of the risk of bias (RoB) in included studies. Cochrane systematic reviews are considered the golden standard regarding systematic review methodology, but Cochrane's instructions for assessing the risk of attrition bias are vague, which may lead to inconsistencies in authors' assessments. The aim of this doctoral dissertation was to conduct three studies, to analyze the consistency of judgments and related explanations for domains attrition bias and other bias, as well analyze methods of assessing 'overall bias' in Cochrane reviews of interventions published in the Cochrane Database of Systematic Reviews (CDSR), and sensitivity analyses related to overall RoB.

Methods: The analysis included Cochrane reviews of interventions that included randomized controlled trials (RCTs) and were published from July 2015 to June 2016 and for the third study from July 2015 to June 2018 in the CDSR. The following data were extracted: the number of included trials, the judgment of attrition, and other risk of bias for each included trial (low, unclear, or high) and accompanying support for the judgment (supporting explanation). We also assessed how many Cochrane reviews had different judgments for the same supporting explanations. We extracted data regarding methods for judging overall bias on a trial level and details regarding methods used for using RoB in sensitivity analyses. Descriptive statistics was used.

Results: *The first study:* In the principal analysis, we included 10292 judgments and supporting explanations for attrition bias from 729 Cochrane reviews. We categorized supporting explanations for those judgments into four categories, and we found that most of the supporting explanations were unclear. Numerical indicators for percent of attrition and statistics related to attrition were judged very differently. One-third of Cochrane reviews had more than one category of supporting explanation; some had up to four different categories. Inconsistencies were found

even with the number of judgments, names of risk of bias domains, and different judgments for the same supporting explanations in the same Cochrane review. *The second study:* We analyzed 768 Cochrane reviews that included 11369 RCTs. There were 602 (78%) Cochrane reviews that had 'other bias' domain in the RoB tool, and they included a total of 7811 RCTs. In the RoB table of 337 Cochrane reviews for at least one of the included trials, it was indicated that no other bias was found, and supporting explanations were inconsistently judged as low, unclear, or high RoB. In the 524 Cochrane reviews that described various sources of other bias, there were 5762 individual types of explanations which we categorized into 31 groups. The judgments of the same supporting explanations were highly inconsistent. We found numerous other inconsistencies in reporting of sources of other bias in Cochrane reviews. *The third study:* Of 1452 analyzed Cochrane reviews, 409 mentioned assessment of overall RoB on a study level. In 107 reviews, authors specified key domains that determined the overall RoB, while in the remaining reviews, assessment of overall bias was not in line with the Cochrane Handbook. Among 268 Cochrane reviews that had any RoB-related sensitivity analysis, in 56 (21%) reviews, the authors reported a significant change for at least one outcome compared to the initial analysis.

Conclusion: We found very high inconsistency in methods of appraising risk of attrition and other bias in recent Cochrane reviews. Highly heterogeneous approaches to summarizing overall RoB on a study level and using RoB for sensitivity analyses may yield inconsistent and incomparable results across Cochrane reviews. Systematic review authors need clear guidance about the assessment of different domains of RoB. Clear instructions about appraising RoB will improve the reliability of the Cochrane's risk of bias tool, help authors in making decisions about the risk of bias, and help in making reliable decisions in healthcare.

11. ŽIVOTOPIS

EUROPEAN CURRICULUM VITAE FORMAT

OSOBNI PODACI

Ime i prezime	**Andrija Babić**
Adresa	Spinčićeva 1, 21000 Split
Elektronička pošta	babic.andro@gmail.com, andrija.babic@zhmsdz.hr
Državljanstvo	Republike Hrvatske
Datum rođenja	13. travnja 1988.
Bračni status	oženjen, otac troje djece

RADNO ISKUSTVO

• Datumi (od – do)	Siječanj 2019.– danas
Ustanova zaposlenja	Medicinski fakultet Sveučilišta u Splitu
Naziv radnog mjesta	Asistent na Katedri za kliničke vještine

• Datumi (od – do)	Lipanj 2018.– danas
Ustanova zaposlenja	Zavod za hitnu medicinu Dubrovačko- neretvanske županije
Naziv radnog mjesta	Liječnik u hitnoj helikopterskoj medicinskoj službi

• Datumi (od – do)	Prosinac 2017.– danas
Ustanova zaposlenja	Zavod za hitnu medicinu Splitsko- dalmatinske županije
Naziv radnog mjesta	Specijalizant hitne medicine

• Datumi (od – do)	Svibanj 2014.– Prosinac 2017.
Ustanova zaposlenja	Zavod za hitnu medicinu Splitsko- dalmatinske županije, Ispostava Vrgorac
Naziv radnog mjesta	Doktor medicine u Timu 1 hitne medicine

• Datumi (od – do)	Studeni 2013.– Travanj 2014.
Ustanova zaposlenja	Klinički bolnički centar Split
Naziv radnog mjesta	Obvezni pripravnički staž za doktore medicine

ŠKOLOVANJE

Datum	Studeni 2016.- danas
Mjesto	Split, Hrvatska
Ustanova	Sveučilište u Splitu, Medicinski fakultet
Zvanje	Poslijediplomski doktorski studij Translacijska istaživanja u biomedicini (TRIBE), student

Datum	Listopad 2006.– Travanj 2013.
Mjesto	Split, Hrvatska
Ustanova	Sveučilište u Splitu, Medicinski fakultet
Zvanje	Doktor medicine

NAGRADE I PRIZNANJA

Zahvalnica KBC-a Split za rad u vrijeme pandemije COVID-19- 2020.

USAVRŠAVANJA

1) Tečaj naprednog održavanja života (ALS). Split, Hrvatska. 21.-23. listopada 2016.

2) Hitnosti u kliničkoj medicini. Zagreb, Hrvatska. 06.-08. travnja 2017.

3) Tečaj za osposobljavanje kandidata za nacionalne instruktore. Donja Stubica, Hrvatska. 22.-24. veljače 2018.

4) Hitna stanja u djece. Imotski, Hrvatska. 07. travnja 2018.

5) Međunarodni skup „Praktična znanja za studente". Split, Hrvatska. 4.-7. travnja 2019. Voditelj radionice.

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7) Tečaj naprednog održavanja života djece (APLS). Split, Hrvatska. 27.-29. rujna 2019. Predložen za instruktora.

8) Škola hitne medicine, Modul 1: Kardiocirkulacijski i respiracijski poremećaji, Zagreb, Hrvatska, 22.-23. studenog 2019.

9) 12. hrvatski Cochrane simpozij. Split, Hrvatska. 03. studenog 2020.

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RECENZIJE

Vanjski recenzent za časopise *BMC Medical Research Methodology* i *Research Methods in Medicine & Health Sciences*

JEZICI

Hrvatski (materinji jezik)

Engleski (aktivno)

Talijanski (pasivno)

ČLANSTVA U STRUČNIM DRUŠTVIMA	Europsko društvo za hitnu medicinu 2020.-danas Hrvatski Cochrane 2019.-danas Hrvatsko društvo za hitnu medicinu 2017.-danas Hrvatski liječnički zbor 2016.-danas Hrvatska liječnička komora 2014.-danas
OSTALA ČLANSTVA I AKTIVNOSTI	Pastoralno vijeće župe Gospe u Siti, koordinator, 2021.-danas Vijeće roditelja Osnovne škole Strožanac, član, školska godina 2020./2021. Upravni odbor muškog pjevačkog zbora „Splitski liječnici pjevači“, član, 2020.-danas Župa Gospe u Siti, župni suradnik, 2018.-2021. Muški pjevački zbor „Splitski liječnici pjevači“ 2009.-danas Franjevačka mladež 2002.-2008.
STUDENTSKE I ŠKOLSKE AKTIVNOSTI	Akademske godine 2011./2012. – Član Savjeta Sveučilišta u Splitu Akademske godine 2010./2011. i 2011./2012. – Predsjednik Odbora za društvene aktivnosti Studentskog zbora Sveučilišta u Splitu Akademske godine 2010./2011. i 2011./2012. – Član Fakultetskog vijeća te Dekanskog kolegija Medicinskog fakulteta Sveučilišta u Splitu Akademske godine 2010./2011. – Član Povjerenstva za praćenje kvalitete nastave Medicinskog fakulteta Sveučilišta u Splitu Akademske godine 2010./2011. i 2011./2012. – Predsjednik Studentskog zbora Medicinskog fakulteta Sveučilišta u Splitu Akademske godine 2008./2009. i 2009./2010. – Član uredništva Glasnika Medicinskog fakulteta Sveučilišta u Splitu Akademske godine 2007./2008., 2008./2009. i 2009./2010. – Demonstrator na Katedri za anatomiju Medicinskog fakulteta Sveučilišta u Splitu Školska godina 2005./2006. - Predsjednik Učeničkog vijeća Gimnazije „Dr. Mate Ujevića“ Imotski

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13. RADOVI OBJEDINJENI U DISERTACIJI

13.1 Prvi rad

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BMC Medical Research Methodology

RESEARCH ARTICLE Open Access

Assessments of attrition bias in Cochrane systematic reviews are highly inconsistent and thus hindering trial comparability

Andrija Babic[1], Ruzica Tokalic[2], João Amílcar Silva Cunha[3], Ivana Novak[2], Jelena Suto[2], Marin Vidak[2], Ivana Miosic[2], Ivana Vuka[2], Tina Poklepovic Pericic[2] and Livia Puljak[4*]

Abstract

Background: An important part of the systematic review methodology is appraisal of the risk of bias in included studies. Cochrane systematic reviews are considered golden standard regarding systematic review methodology, but Cochrane's instructions for assessing risk of attrition bias are vague, which may lead to inconsistencies in authors' assessments. The aim of this study was to analyze consistency of judgments and support for judgments of attrition bias in Cochrane reviews of interventions published in the Cochrane Database of Systematic Reviews (CDSR).

Methods: We analyzed Cochrane reviews published from July 2015 to June 2016 in the CDSR. We extracted data on number of included trials, judgment of attrition risk of bias for each included trial (low, unclear or high) and accompanying support for the judgment (supporting explanation). We also assessed how many Cochrane reviews had different judgments for the same supporting explanations.

Results: In the main analysis we included 10,292 judgments and supporting explanations for attrition bias from 729 Cochrane reviews. We categorized supporting explanations for those judgments into four categories and we found that most of the supporting explanations were unclear. Numerical indicators for percent of attrition, as well as statistics related to attrition were judged very differently. One third of Cochrane review authors had more than one category of supporting explanation; some had up to four different categories. Inconsistencies were found even with the number of judgments, names of risk of bias domains and different judgments for the same supporting explanations in the same Cochrane review.

Conclusion: We found very high inconsistency in methods of appraising risk of attrition bias in recent Cochrane reviews. Systematic review authors need clear guidance about different categories they should assess and judgments for those explanations. Clear instructions about appraising risk of attrition bias will improve reliability of the Cochrane's risk of bias tool, help authors in making decisions about risk of bias and help in making reliable decisions in healthcare.

Keywords: Systematic review, Cochrane, Attrition bias, Incomplete data, Missing data, Inconsistency

Background

Cochrane systematic reviews are produced using rigorous and evolving methodological standards and are therefore considered the gold standard when it comes to synthesis of evidence. The Cochrane has been at the forefront of applying the methods of evidence-based medicine (EBM) in the treatment and management of various conditions [1].

An important part of the systematic review methodology is appraisal of the risk of bias (RoB) in included studies. The potential effect of bias is that trialists will reach wrong conclusions about efficacy and safety of studied interventions. Bias can, therefore, negatively affect the estimated intervention effects [2].

In Cochrane systematic reviews RoB is appraised using Cochrane RoB tool, which has seven domains; one of them is called 'incomplete outcome data (attrition bias)'. Incomplete outcome data can yield attrition bias due to amount, nature or handling of incomplete outcome

* Correspondence: livia.puljak@unicath.hr; livia.puljak@gmail.com
[4]Center for Evidence-Based Medicine and Health Care, Catholic University of Croatia, Ilica 242, 10000 Zagreb, Croatia
Full list of author information is available at the end of the article

data [3]. The main strength of RCTs is that study arms should generally be balanced in terms of their baseline characteristics, and any imbalance should be result of chance. Attrition can occur if participants are lost to follow-up, or if they miss one or more measurement time points during a trial. Therefore, attrition can lead to bias if the characteristics of participants with missing data are different between the randomized groups [4]. Akl et al. analyzed potential impact of losses to follow-up on the estimates of the effect of treatment in 235 RCTs, and found that different assumptions about outcomes of participants lost to follow-up could change interpretation of results of up to 58% of RCTs published in top medical journals, and a third of the analyzed trials failed to report whether any loss to follow-up occurred [5].

In the Cochrane RoB tool, the authors need to provide judgment about whether this risk is high, unclear or low for each domain. Furthermore, each judgment needs to be accompanied with a supporting explanation called 'support for judgment', which *"describes what was reported to have happened in the study, in sufficient detail to support a judgment about the risk of bias"*. The aim of the support for judgment is to ensure transparency about how these judgments about the level of risk of bias were reached [3].

The Cochrane Handbook provides vague instructions about assessing attrition bias, which may lead to inconsistent use of supporting explanations for judgments of attrition bias that one can find in Cochrane reviews. Da Costa et al. have published a study in 2017 about training authors for risk of bias assessment, and showed that *"Kappa values between the minimal training group and reference across items of the risk of bias tool ranged from 0.10 (poor agreement) for incomplete outcome data (…)"* [6]. Therefore, inter-rater agreement in participants with minimal training was worst for the attrition bias domain, compared to other domains of Cochrane RoB. Since Cochrane authors rarely have structured training that was tested in the study of da Costa et al. [6], their data could very well indicate real-world difficulties and discrepancies that authors face when assessing attrition bias.

The aim of this study was to analyze whether Cochrane authors use consistent judgments for different supporting explanations of attrition bias in Cochrane reviews of interventions published in the Cochrane Database of Systematic Reviews (CDSR).

Methods

Study design

This was a cross-sectional, primary methodological study in which we analyzed methods of published Cochrane reviews.

Inclusion and exclusion criteria

Cochrane reviews of interventions published from July 2015 to June 2016 were included by using Advanced search in The Cochrane Library. We excluded diagnostic reviews, empty reviews, overviews of systematic reviews and Cochrane reviews withdrawn in this period and reviews that included only non-randomized studies. If the Cochrane reviews included randomized, quasi-randomized and non-randomized studies, we analyzed attrition bias in the RoB tables for the randomized studies only. Cochrane reviews that had multiple attrition bias judgments assessed for different outcomes in the same study were rare; therefore we reported them separately in order to better describe that methodological approach.

Screening

Two authors (JASC, LP) independently assessed all titles/abstracts to establish eligibility of Cochrane reviews for inclusion. There were no discrepancies in judgment.

Data extraction

Data extraction table was developed and piloted using five Cochrane reviews. Seven authors extracted data manually (RT, JASC, IN, JS, MV, IM, IV) and initially another author (AB) checked 10% of the extractions randomly. Discrepancies in data extraction were planned to be resolved by the third author (LP), but we found only several discrepancies, which did not require adjudication by the third author. In 2018, for the purpose of another project we developed customized software acting as a parsing tool, which can extract clearly delimited information from Cochrane reviews. Using the parsing tool, we extracted again the same data for attrition bias from the Cochrane RoB table, and found only 34 discrepancies that needed to be corrected.

The following data were extracted: number of included trials, judgment of attrition risk of bias for each included trial (low, unclear or high) and accompanying 'support for judgment'. To avoid terminological confusions, instead of 'support for judgment' hereby we use the expression 'supporting explanation'. We also assessed how many Cochrane reviews had inconsistent judgments for the same supporting explanations (i.e. whether they had different judgments for the same supporting explanations). In the main analysis we reported only analysis of attrition bias for included Cochrane reviews with a single judgment (i.e. Cochrane reviews with only one domain for attrition bias, and one judgment in that one domain), regardless of the number of supporting explanations that were provided for that judgment.

In the secondary analysis we investigated i) attrition bias reporting for Cochrane reviews that reported multiple judgments of attrition bias for the same trial (i.e.

Cochrane reviews with multiple assessments of attrition bias for the same RCT, where this RoB domain was split into two or more sub-domains analyzing specific aspects of attrition bias), ii) characteristics of risk of bias reporting in Cochrane reviews that did not have attrition bias domain, and iii) characteristics of risk of bias judgment reporting in Cochrane reviews that did not provide judgment in the form of "low, unclear and high". Specific Cochrane reviews are marked in the body of this manuscript with the serial number of the downloaded record (for example, Cochrane review #1). A list of included and excluded studies with a serial number of each record is in the Additional file 1: Table S1.

Statistics

Descriptive statistics was performed and data presented as frequencies and percentages. Data were analyzed using Microsoft Excel (Microsoft Inc., Redmond, WA, USA).

Results

Among 955 Cochrane systematic reviews published from July 2015 to June 2016 we included 729 Cochrane reviews in the main analysis. In the 729 included reviews there were 1–105 included studies (median: 8 studies). In those reviews we found 10,292 attrition bias domains with single judgment about whether the Cochrane review authors found this bias to be low, unclear or high. Although there was a single judgment, 3504/10292 (34%) supporting explanations contained more than one type of explanations related to risk of attrition bias. We categorized these different types of supporting explanations into four categories: #1: percent of attrition in the RCT groups with higher attrition, #2: difference in attrition between the groups, #3: reporting of reasons for attrition and #4: statistical comments. Only 27/10292 (0.26%) of supporting explanations had all four categories of explanations.

First category: percent of attrition in the RCT groups with higher attrition

In the first category, called 'percent of attrition in the RCT groups with higher attrition' a third of supporting explanations were unclear (32%). While there were too many examples of unclear explanations, we provide some examples of explanations categorized by us as unclear explanations in the Table 1. The next most common type of supporting explanations were mentioning only total attrition (16%), indicating there was no attrition (15%) in the trial, providing only number of patients without a percent (11%), or indicating that attrition was not reported in a trial (8.8%) (Table 2).

We categorized reported percent of attrition in the group with higher attrition into four categories: attrition under 10%, between 10 and 20%, between 21 and 30% and above 30%. Since some Cochrane reviews had multiple supporting explanations for a single judgment, we analyzed separately only reviews where the only supporting explanation was about percent of attrition in the study groups (Table 3). The purpose of this analysis was to see whether Cochrane authors use consistent judgments for various thresholds of attrition in this category of supporting explanations. In the Table 3 we listed total number of Cochrane reviews that had supporting explanations related to percent of attrition in the RCT groups with higher attrition. However, on the right side of the Table 3 we presented data only for reviews where the only supporting explanation was about percent of attrition in the study group because only for these Cochrane reviews we can be sure that the single judgment applies only to that comment. As Table 3 indicates, Cochrane authors use very heterogeneous judgments for each category of comment.

Table 1 Examples of unclear supporting explanations

Study number	Unclear supporting explanation	Judgment
2	All participants were accounted for	Low
12	Outcomes reported for all women randomized	Low
20	Primary outcomes were reported	Low
26	None found	Low
54	Analysed the same number of participants in both groups	Low
66	Expected outcomes reported. Response rates reduced in patients over 4 surveys	Low
80	No study protocol was available	Low
82	It appears that all participants completed the study and contributed data for each outcome at all relevant time points	Low
2	Unclear	Unclear
4	Losses to follow-up were unclear	Unclear
6	It was unclear whether or not there was attrition, or loss to follow-up at final follow-up based on the results section	Unclear
29	No information	Unclear
31	Insufficient information to permit judgment of low risk or high risk	Unclear
32	May be participants randomized who did not complete	Unclear
41	Few data available in conference abstract only	Unclear
66	Unknown	Unclear
442	High attrition (41%)	Unclear
13	Number of drop-outs reported, but no details	High
25	Not all raw data were provided	High
52	Not clear how many withdrew	High

Table 2 Number of explanations in a category for percent of attrition per group

Category for percent of attrition per group	N (%)
Unclear	3272 (31.8)
Total attrition only mentioned; attrition per group not reported	1593 (15.5)
No attrition	1544 (15)
Only number of patients, no percent provided	1115 (10.8)
Not reported	901 (8.8)
No explanation for this category	414 (4)
10–20%	359 (3.5)
Above 30%	276 (2.7)
Under 10%	267 (2.6)
20–30%	216 (2.1)
Total attrition reported as percent; attrition per group reported as absolute numbers so it was not possible to judge percent attrition per group	248 (2.4)
Information about attrition provided for one group only	35 (0.3)
'Support for judgment' box was blank: no explanation provided for the judgment	27 (0.3)
Above certain percentage that is not precisely defined	13 (0.1)
Under certain percentage that is not 10%	6 (0.06)
There was no supporting explanation because RoB table did not have a domain for attrition bias at all	6 (0.06)
Total	10,292 (100)

Second category: difference in attrition between the groups

In the second category of supporting explanations about difference in attrition between the groups, 302/10292 (2.9%) explanations reported this category, and in all of them it was reported if the difference was above 10%.

Third category: reporting of reasons for attrition

There were 2157/10292 (21%) supporting explanations related to reasons for attrition. The majority of these explanations referred to reasons for attrition that were reported in a trial, while the remaining supporting explanations indicated either that reasons for attrition were not reported in a trial, or that they were inadequately reported (Table 4).

Fourth category: supporting explanations about statistics

We found 1572/10292 (15.3%) supporting explanations related to statistics; Table 5 lists all of them in a way that they were described by the Cochrane review authors themselves. Most of the explanations about statistics were referring to presence or absence of intention-to treat analysis (ITT), per protocol analysis (PP) or last observation carried forward (LOCF) (Table 5). Detailed analysis of risk of bias judgment categories was shown only for the most commonly used categories that reported only supporting explanation about statistics; for each statistical comment, Cochrane authors had highly heterogeneous judgments regarding their impact on risk of attrition bias (Table 3).

There were 35 Cochrane reviews that indicated that it was unclear whether ITT analysis was used or not, because its usage was not described. We did not analyze this group of CRSs because none of those listed this item as the only supporting explanation for risk of attrition bias judgment.

Inconsistencies in judgments in single Cochrane reviews

We found only 34/729 (4.7%) Cochrane reviews that had inconsistencies in judging risk of attrition bias in the same review. This means that they gave different

Table 3 Frequency of different judgments for the same supporting explanation related to percent of attrition in RCT groups and comments about statistics

Supporting explanation *n* = total number of Cochrane reviews that had this supporting explanation *N* = number of analyzed Cochrane reviews	Risk of bias judgment		
	Low, N (%)	Unclear, N (%)	High, N (%)
Percent of attrition in the RCT groups with higher attrition			
Attrition between the groups was under 10%, *n* = 264, *N* = 122	101 (82.8)	16 (13.1)	5 (4.1)
Attrition between the groups that was 10–20%, *n* = 354, *N* = 143	91 (63.6)	28 (19.6)	24 (16.8)
Attrition between the groups that was 21–30%, *n* = 215, *N* = 60	34 (56.7)	5 (8.3)	21 (35)
Attrition between the groups that was above 30%, *n* = 276, *N* = 70	18 (25.7)	9 (12.9)	43 (61.4)
Supporting explanations about statistics			
ITT analysis used, *n* = 825, *N* = 193	140 (72.5)	21 (10.9)	32 (16.6)
ITT analysis was not used, *n* = 238, N = 35	20 (57.1)	9 (25.7)	6 (17.1)
PP analysis used, *n* = 81, N = 8	7 (87.5)	1 (12.5)	0 (0)
LOCF analysis used, *n* = 66, *N* = 25	13 (52)	3 (12)	9 (36)

Abbreviations: ITT intention-to-treat, *LOCF* last observation carried forward, *PP* per protocol, *RCT* randomized controlled trial,

Table 4 Number of supporting explanations in a category for reporting reasons for attrition

Category: reporting of reasons for attrition	N (%)
Reasons reported	1697 (16.5)
Reasons not reported	370 (3.6)
Inadequately reported	90 (0.9)
Total	2157 (21)

judgment for the same explanation. For example, "No incomplete outcome data" was judged as either low or unclear risk of bias in the review #210. In the review #255 explanation "No pre-publication protocol identified" was judged either as unclear or high. In the review #277 "No missing data" was judged as low or unclear. In the review #330 "No withdrawals mentioned" was judged as either low or unclear risk of attrition bias. There were 66/729 (9.1%) Cochrane reviews for which this analysis was not applicable because they included only one trial. All the other reviews had consistent judgments for the given supporting explanations.

Secondary analysis: studies with multiple judgments of attrition bias for the same study

We found 27 Cochrane reviews that had multiple assessments of attrition bias for the same RCT. They had 2–7 multiple assessments separately, which we categorized in assessments related to aspects of attrition bias, time, objectivity and clinical outcomes.

Five Cochrane reviews had separate assessments of different aspects of attrition bias were assessments of drop-outs, participants analyzed in the group to which they were allocated and whether ITT analysis was performed. Seven reviews had assessments related to time were multiple assessments for short-term or long-term outcomes, sometimes defined with specific time-frame (i.e. before or after 12 weeks or childhood outcomes), or end-of-intervention and end of follow-up. Five Cochrane reviews had separate assessments for subjective and objective outcomes. One of them specified what was a subjective and what an objective outcome was. Ten reviews had separate assessments for different clinical outcomes (Table 6). The review authors did not analyze all these sub-domains for all studies included in those reviews.

Cochrane reviews that did not have a domain for attrition bias in the RoB table

There were 12 Cochrane reviews that did not have a domain for attrition bias at all in the RoB table. They were not included in the main analysis, and hereby we report characteristics of their RoB tables. Five reviews analyzed only 1 RoB domain, and this was 'Allocation concealment in four cases (reviews #341, #465, #672 and #904) and 'Method for selecting cases to adjudicate?' in one case (reviews #269). One review analyzed 3 RoB domains (Random sequence generation, Allocation concealment and Blinding as one domain for all outcomes), but not attrition bias (review #294). Three reviews analyzed 4 RoB domains; one of them analyzed 'Random sequence generation', 'Allocation concealment', 'Blinding of outcome assessment', 'Selective reporting' (review #585) and two analyzed domains for 'Random sequence generation', 'Allocation concealment', 'Blinding of participants and personnel (performance bias)', 'Size' (review #924, #936). Two Cochrane reviews analyzed five RoB domains (review #174, #947) and one analyzed six RoB domains – but none of the domains were attrition bias (review #309).

Risk of bias assessed with 'yes' or 'no' judgments

In 4/729 Cochrane reviews (0.5%) there was no standard judgment of risk of bias as high, unclear or low; instead RoB was judged as yes, unclear, no, or yes/no (reviews #212, #292, #830 and #884). In one review risk of bias was graded as "low, unclear or high", but in the supporting explanation also rated as A – Adequate, B – Unclear, C – Inadequate (review #244).

Other inconsistencies that were encountered

Several Cochrane reviews had different name of the relevant domain. In the review #641 the domain was called "Intention-to-treat analysis performed?", in the #419 "Losses to follow-up taken into account?" and in the review #873 "Complete follow-up?"

Explanations that should not be used for judging attrition bias

Finally, we decided to report examples of curious explanations for attrition bias judgments in Table 7. It appears to us that such explanations should not be used for explaining risk of attrition bias judgments.

Discussion

We found high inconsistency in the assessment of risk of bias related to incomplete outcome data, i.e. attrition bias in Cochrane systematic reviews. Cochrane authors do not have uniform approach to judging attrition bias. We did not observe clear numerical rules about the percent of attrition in trial groups or clear rules about statistics that was used or not used, that were consistently labeled as low, unclear or high risk of bias. One third of Cochrane review authors had more than one category of explanations; some had up to four different categories. Inconsistencies were found even with the number of judgments, names of risk of bias domains and different judgments for the same explanations in the same review.

Cochrane Handbook indicates that "*Missing outcome data, due to attrition (drop-out) during the study or*

Table 5 Supporting explanations about statistics used that was related to attrition bias

Statistical information	N (%)
ITT	826 (8)
No ITT	238 (2.3)
PP	88 (0.9)
ITT, LOCF	87 (0.8)
LOCF	67 (0.7)
ITT not reported	47 (0.5)
ITT, PP	34 (0.3)
Completer analysis	27 (0.2)
mITT	25 (0.2)
Sensitivity analysis	15 (0.1)
BOCF	12 (0.1)
ITT, BOCF	8 (0.08)
Analysis not described	6 (0.06)
Available case analysis	5 (0.05)
ITT, Completer analysis	5 (0.05)
LOCF, BOCF	5 (0.05)
ITT analysis may have been of value	4 (0.04)
ITT, PP, LOCF	4 (0.04)
ITT, LOCF, WOCF	4 (0.04)
LOCF, PP	4 (0.04)
Partial ITT	4 (0.04)
WOCF	3 (0.03)
Unclear whether LOCF was used	3 (0.03)
ITT inadequate	3 (0.03)
Some participants were excluded from analysis	3 (0.03)
No ITT, PP	3 (0.03)
BOCF, WOCF	2 (0.02)
ITT, LOCF, NRI	2 (0.02)
No LOCF	2 (0.02)
We have not been able to re-analyse the outcomes for all of the enrolled infants (ITT)	1 (0.01)
LOCF, Sensitivity analysis	1 (0.01)
ITT, PP, LOCF, Sensitivity analysis	1 (0.01)
The trial states that the analysis was performed on an ITT basis, but the data seems to have been analysed on-treatment	1 (0.01)
ITT analysis possible	1 (0.01)
ITT analysis conducted but unclear how missing data were dealt with	1 (0.01)
PP, FAS	1 (0.01)
It is likely that the principle of ITT analysis was violated	1 (0.01)
Statistical analysis used the APT	1 (0.01)
Missing outcome data imputed in analysis	1 (0.01)
True ITT analysis was difficult	1 (0.01)
Missing participants were omitted from the analysis	1 (0.01)
Although the study was set up to be analysed on ITT basis, the participants with missing outcomes were not included in the primary analysis	1 (0.01)
ITT done only for *P* value	1 (0.01)
Not strict ITT analysis	1 (0.01)
mITT, but unclear how missing data were dealt with	1 (0.01)
ITT, WOCF	1 (0.01)
mITT, LOCF	1 (0.01)
mITT, PP	1 (0.01)
Equal distribution among groups, ITT analysis not necessary	1 (0.01)
It was unclear if data analysis was PP or ITT	1 (0.01)
The results are presented as available case analysis rather than ITT. The authors present a sensitivity analysis	1 (0.01)
No information about whether an ITT analysis was undertaken and, if so, how missing data were imputed	1 (0.01)
This is an "as treated" as opposed to an ITT analysis	1 (0.01)
LOCF, BOCF, SOCF	1 (0.01)
ITT, PP, mITT	1 (0.01)
ITT, No sensitivity analysis	1 (0.01)
LOCF, Completer analysis	1 (0.01)
Large number of cross-overs made ITT impossible after the first phase	1 (0.01)
Unclear if ITT	1 (0.01)
ITT, PP, Sensitivity analysis	1 (0.01)
No ITT, Completer analysis	1 (0.01)
No mention of how missing data from participants who dropped out were dealt with, e.g. ITT analysis	1 (0.01)
ITT, Sensitivity analysis	1 (0.01)
No sensitivity analysis	1 (0.01)
LOCF, WOCF	1 (0.01)

Abbreviations: *ITT* intention-to-treat analysis, *PP* per protocol analysis, *LOCF* last observation carried forward, *mITT* modified intention-to-treat analysis, *BOCF* baseline observation carried forward, *WOCF* worst observation carried forward, *NRI* non-responder imputation, *FAS* full analysis set, *APT* all patients treated, *SOCF* screening observation carried forward

exclusions from the analysis, raise the possibility that the observed effect estimate is biased." The term attrition bias is used for both exclusions and attrition [3]. Besides numerical indicators of attrition – absolute numbers and frequencies – that provide information about the magnitude of attrition, in the context of this domain of risk of bias different statistical methods for imputing missing data are often mentioned. For example, trial authors can use ITT analysis, or a 'modified ITT analysis'. However, it has been reported that the term 'ITT analysis' does

Table 6 Description of domains in Cochrane reviews that had multiple separate domains for assessing attrition bias for different outcomes

Study number	Names of separate domains for attrition bias in the Risk of Bias table
158, 197	Short-term, long-term
240	End-of-intervention, end of follow-up
250, 459, 533	Subjective outcome measures, objective outcome measures
285	Clinical heart failure, subclinical heart failure (dichotomous and/or continuous), overall survival, tumor response, quality of life, adverse effects, adverse effects other than cardiac damage
302	Drop-out rate described and acceptable, participants analyzed in the group to which they were allocated
312	Mortality (all cause), hospital readmissions (all cause), hospital readmissions (due to adverse drug events), hospital emergency department contacts (all-cause), hospital emergency department contacts (due to adverse drug events), adverse drug events
316	Adverse events: hypothyroidism, development or worsening of Graves' ophthalmopathy, health-related quality of life, participants in euthyroid state, recurrence of hyperthyroidism, socioeconomic effects
324	12 weeks or less, after 12 weeks
340	Primary outcomes, secondary outcomes
346	All outcomes: drop-outs, all outcomes: ITT analysis
394	Time to resolution of diabetic ketoacidosis, all-cause mortality, hypoglycemic episodes, morbidity, socioeconomic effects
427	Drop-outs reported, ITT analysis reported
499	Objective outcome (deaths), subjective outcome (quality of life)
638, 795	Drop-outs, ITT analysis
641	Pain, function
722	Short term follow-up (up to 3 months), longer term follow-up
761	Consumption outcome, selection outcome
805	Hemodynamic data, clinical outcomes
867	Survival, tumor response, toxicity, quality of life
943	Short-term outcomes, childhood outcomes
946	All outcomes, ITT analysis
949	Wound healed, wound area, time to healing
951	Pain, swelling, function, adverse effects

not always have a clear and consistent definition, and that it is not consistently used in trial reports [7]. The same was concluded for the modified ITT analysis and therefore it has been recommended by the Cochrane Handbook that the review authors should always ask information about who exactly was included in such analysis [3]. Simple imputations, such as last observation carried forward (LOCF) remain very popular despite warnings of statisticians against their use [8].

Judgments about different statistical methods varied in our analysis; we found very inconsistent judgments for different statistical methods. If we want to judge by the frequency of statistical comments in reviews where this was the only available explanation, we could not reach any conclusion, because the majority of authors judged presence of ITT analysis with low risk of bias, but also in the group that reported explicitly that there was no ITT analysis, this absence of ITT analysis was also predominantly judged with low risk of bias. Using *per protocol* analysis was mostly judged as low risk of bias, as well as LOCF analysis.

It has been published previously that attrition under 5% is not likely to introduce bias, while attrition rates above 20% raise concerns about the study validity [9]. While Cochrane handbook does not give clear guidance about the total attrition or attrition per group regarding specific numerical values, there is an example in the Fig. 8.6.a. in that handbook: "*17/110 missing from intervention group (9 due to 'lack of efficacy'); 7/113 missing from control group (2 due to 'lack of efficacy')*" that is judged as high risk [3]; in this example the first group has attrition of 15%. If a Cochrane author should follow this example, then attrition that is 15% or above per group should be labeled as high risk of bias. In Table 8, we present examples of vague instructions for Cochrane authors regarding judgments of attrition bias, in line with the current instructions for judging attrition bias that are available in the Cochrane Handbook in Table 8.5.d., which gives authors instructions about specific situations where each domain should be judged as low, unclear or high [3].

In our study we found that numerical indicators for what represents attrition were widely inconsistent. When we categorized reported percent of attrition in the group with higher attrition and which threshold was predominantly judged in a certain way, attrition in a group that was under 10% was judged as low risk of bias in 83% of the cases, attrition 10–20% was judged as low risk of bias in 64% of cases, attrition 20–30% was judged as low risk of bias in 57% of cases. If we judge from the majority opinion of Cochrane authors, threshold of 'above 30% is considered predominantly high risk of bias because 61% of judgments indicated so in Cochrane reviews where this was the only judgment so we could isolate the effect of this category for the overall judgment.

As for the risk of bias as a tool, it has been reported that it has low reliability between individual reviewers and across consensus assessments of reviewer pairs [10]. It has been argued that low reliability of the RoB assessment can have negative effects on decision making and quality of health care [11]. It has also been shown by da Costa et al. that standardized intensive training on RoB assessment may significantly improve the reliability of

Table 7 Examples of curious supporting explanations for attrition bias judgments that may not appear to be suitable for judging this risk of bias domain

Study number	Support for judgment	Judgment for risk of attrition bias
82	Chinese article - unable to ascertain	Unclear
144	This study was a feasibility study. Only 1 woman received the intervention. This study contributed no data to the review.	Unclear
255	No pre-published protocol identified	High or unclear
256	If we assume a person works for 40 h per week, then for 28 participants the working hours will be 8960 h for 8 weeks (4 weeks intervention and 4 weeks control period). However the study reported only 7729 working hours based on accelerometer data	High
376	This is not clear from the paper. Author contacted, but when he moved jobs, the data files for this study were deleted	Unclear
490	137 minus 28 equals 109, not 108	Unclear
492	Exact time periods of 'before and after' accident data were unclear. Authors reported that they "should be 3 to 5 years".	Unclear
494	1 - A reasonable account of how attrition was dealt with is given, but no specific reference to CONSORT	Low
517	Documented evidence that the CONSORT guidelines have been followed	Low
606	Data sparse largely narrative style	Unclear
699	Numbers do not always add up - query if N for outcomes are based on those who answered specific questions on follow-up?	High
727	Data of drop-outs was censored.	Low
730	Eleven patients were withdrawn before random assignment: 1 declined further participation, 8 were withdrawn by their physician, and 2 did not meet the entry criteria	Low
744	Publication is in German and our translation is incomplete.	Unclear
835	Differences in baseline characteristics of questionnaire responders vs non-responders (western ethnicity in 81% vs 54%, mean age 31 vs 28 years, median blood loss 1500 vs 1150 mL). Big difference in compliance to allocated treatment: 8 vs 34. The design of this trial carries a high risk for selecting the study population	High
838	Primary and secondary endpoints not specified directly but do address aims	Low
849	"The situations to consider eliminating the subject from data analysis did not arise"	Low
850	No Table 1 to clearly describe participant characteristics.	High
854	Duration of study not defined	High
854	Criteria for kidney disease not defined	Unclear
873	Denominators inconsistent in study	Unclear

Table 8 Examples of vague instructions for Cochrane authors regarding judgments of attrition bias

Quote from a Cochrane review	Comment of authors of this study
Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups	There is no quantitative measure of "balanced"
For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate	There is no quantitative measure of "not enough"
Missing data have been imputed using appropriate methods	Not specified what is considered by Cochrane to be "appropriate methods"
Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups	There is no quantitative measure of "imbalance"
Potentially inappropriate application of simple imputation.	Not specified what is considered to be "inappropriate application"

the Cochrane RoB tool [6]. However, our study points out that we would need first to have standardized instructions about what situations really represent risk of attrition bias. Having clear instructions, such as "attrition above 20% represents high risk of attrition bias" it would be much easier to achieve higher reliability of RoB assessment, even without formal training.

Instructions for assessing risk of attrition bias should include specific indications about all categories of assessment that should be appraised. It should be clearly specified which of those categories systematic review authors should assess, such as four that we used in this manuscript, including percent of attrition per group and difference between the groups, whether reasons for attrition were reported or not, and what is the appropriate statistics for dealing with attrition. If the authors do not have clear guidance about assessment of attrition bias, they can behave as we found – they can use one or more of those categories for their attrition RoB assessment as they personally see fit.

Some authors used multiple judgments for different follow-ups or different outcomes. This also introduces inconsistency in the attrition RoB assessment. Just as the option for authors to change the titles of attrition RoB domains in the RoB table in a Cochrane review.

In our previous analyses of other domains of Cochrane RoB tool in Cochrane reviews have shown that judgments and supports for judgments in those other domains were very inconsistent as well [12–14], further supporting the idea that more attention needs to be devoted to the way authors use this tool.

New version of Cochrane RoB tool, called RoB tool 2.0 is being developed, and its draft version is available online [15]. The draft version of the RoB tool 2.0 has five domains, the domain comparable to the current "Incomplete outcome data (attrition bias)" is the third out of five domains, called "Bias due to missing outcome data". The RoB tool 2.0 has signaling questions in each domain, and this particular domain has three signaling questions [15]. Theoretically, having three signaling questions could help authors to produce three categories of responses, but this will not be the case because some of those signaling questions address more than one category of attrition bias, in the context of categories defined in this manuscript. For example, elaboration for the second signaling question includes both discrepancies in missing data across intervention groups, and reporting reasons for missing data [15].

Furthermore, we consider that this specific domain in the RoB tool 2.0 is not even a step forward in terms of specific instructions to Cochrane authors, because the field "elaboration" of the signaling questions is still as vague as in the current RoB tool, and could be interpreted by Cochrane authors in various ways. The first signaling question is *"3.1 Were outcome data available for all, or nearly all, participants randomized?"*. In the elaboration for the first signaling question there is a phrase *"low or modest amount of missing data"*, but it is not specified what exactly should Cochrane authors consider as "low" and "modest". The elaboration further says *"availability of data from 95% (or possibly 90%) of the participants would often be sufficient"*, but it is unclear what is "often" and when is this not sufficient [15].

The second signaling question is *"Are the proportions of missing outcome data and reasons for missing outcome data similar across intervention groups?"* Elaboration does not give specific instructions about the magnitude of discrepancies; instead it says "*minor degree of discrepancy*" [15].

The third signaling question is "*Is there evidence that results were robust to the presence of missing outcome data?"*, and the elaboration says *"Evidence for robustness may come from how missing data were handled in the analysis and whether sensitivity analyses were performed by the trial investigators, or from additional analyses performed by the systematic reviewers"*. [15]. Again, to us, this elaboration does not give specific instructions to Cochrane authors, and may result in heterogeneous perception and judgment.

Future studies on this topic should explore how to reduce inconsistency in assessment of attrition RoB, and they should attempt to reach consensus about what exactly should be assessed in this RoB domain.

Conclusion

We found very high inconsistency in methods of appraising risk of attrition bias in recent Cochrane reviews. Systematic review authors need clear guidance about different categories they should assess and judgments for those explanations. Clear instructions about appraising risk of attrition bias will improve reliability of the Cochrane risk of bias tool, help authors in making decisions about risk of bias and help in making reliable decisions in healthcare.

Additional file

Additional file 1: Table S1. A list of included and excluded studies with a serial number of each record. The supplementary table contains a full list of included and excluded studies. Data are arranged in four columns. The first column contains a serial number of each study; second column contains title of a review; third column a remark about whether the review was included in the study or not (yes or no); fourth column describes reason for exclusion if a review was not included. (XLSX 65 kb)

Abbreviations

APT: All patients treated; BOCF: Baseline observation carried forward; CDSR: Cochrane Database of Systematic Reviews; EBM: Evidence-based medicine; FAS: Full analysis set; ITT: Intention-to treat analysis; LOCF: Last observation carried forward analysis; mITT: Modified intention-to-treat

analysis; NRI: Non-responder imputation; PP: Per protocol analysis; RCT: Randomized controlled trial; RCTs: Randomized controlled trials; RoB: Risk of bias; SOCF: Screening observation carried forward; WOCF: Worst observation carried forward

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Andrija Babic, Tina Poklepovic Pericic and Livia Puljak are volunteer members of Cochrane Croatia. Livia Puljak is a volunteer section editor of the BMC Medical Research Methodology, but was not involved in any way in handling of this manuscript. All other authors declare they have no competing interests.

Publisher's Note

Author details
[1]Institute of Emergency Medicine in Split-Dalmatia County, Split, Croatia. [2]University of Split School of Medicine, Split, Croatia. [3]Faculty of Medicine, University of Lisbon, Lisbon, Portugal. [4]Center for Evidence-Based Medicine and Health Care, Catholic University of Croatia, Ilica 242, 10000 Zagreb, Croatia.

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The judgement of biases included in the category "other bias" in Cochrane systematic reviews of interventions: a systematic survey

Andrija Babic[1], Andela Pijuk[2], Lucie Brázdilová[3], Yuliyana Georgieva[4], Marco António Raposo Pereira[5], Tina Poklepovic Pericic[2] and Livia Puljak[6*]

Abstract

Background: Clinical decisions are made based on Cochrane reviews, but the implementation of results of evidence syntheses such as Cochrane reviews is problematic if the evidence is not prepared consistently. All systematic reviews should assess the risk of bias (RoB) in included studies, and in Cochrane reviews, this is done by using Cochrane RoB tool. However, the tool is not necessarily applied according to the instructions. In this study, we aimed to determine the types of bias and their corresponding judgements noted in the 'other bias' domain of Cochrane RoB tool.

Methods: We analyzed Cochrane reviews that included randomized controlled trials (RCTs) and extracted data regarding 'other bias' from the RoB table and accompanying support for the judgment. We categorized different types of other bias.

Results: We analyzed 768 Cochrane reviews that included 11,369 RCTs. There were 602 (78%) Cochrane reviews that had 'other bias' domain in the RoB tool, and they included a total of 7811 RCTs. In the RoB table of 337 Cochrane reviews for at least one of the included trials it was indicated that no other bias was found and supporting explanations were inconsistently judged as low, unclear or high RoB. In the 524 Cochrane reviews that described various sources of other bias, there were 5762 individual types of explanations which we categorized into 31 groups. The judgments of the same supporting explanations were highly inconsistent. We found numerous other inconsistencies in reporting of sources of other bias in Cochrane reviews.

Conclusion: Cochrane authors mention a wide range of sources of other bias in the RoB tool and they inconsistently judge the same supporting explanations. Inconsistency in appraising risk of other bias hinders reliability and comparability of Cochrane systematic reviews. Discrepant and erroneous judgments of bias in evidence synthesis may hinder implementation of evidence in routine clinical practice and reduce confidence in otherwise trustworthy sources of information. These results can help authors of Cochrane and non-Cochrane reviews to gain insight into various sources of other bias that can be found in trials, and also to help them avoid mistakes that were recognized in published Cochrane reviews.

Keywords: Systematic review, Cochrane, Risk of bias, Other bias inconsistency

* Correspondence: livia.puljak@gmail.com; livia.puljak@unicath.hr
[6]Catholic University of Croatia, Zagreb, Croatia
Full list of author information is available at the end of the article

Background

Assessment of the risk of bias (RoB) in included studies is an integral part of preparing Cochrane systematic reviews. Bias is any systematic error that can negatively affect the estimated effects of interventions and lead authors to wrong conclusions about efficacy and safety of analyzed interventions [1].

Cochrane reviews use Cochrane's RoB tool, whose aim is to enable better appraisal of evidence and ultimately lead to better healthcare [2]. Cochrane's standard RoB tool has seven domains. First domain addresses random sequence generation as a potential source of selection bias, assessing potentially biased allocation to interventions due to inadequate generation of a randomized sequence. Second domain analyzes allocation concealment, which can also lead to selection bias. The third domain is devoted to blinding of participants and personnel; it is associated with performance bias due to the knowledge of the allocated interventions by participants and personnel during the study. Fourth domain addresses blinding of outcome assessment; if done inadequately, it can lead to detection bias due to the knowledge of the allocated interventions by outcome assessors. Fifth domain analyzes the presence of incomplete outcome data, which can yield attrition bias due to amount, nature or handling of incomplete outcome data. The sixth domain is devoted to selective reporting, which can cause reporting bias due to selective outcome reporting. And finally, there is the seventh domain of Cochrane RoB assessment called "other bias", which is used to note bias occurring due to any additional problems that were not covered by the first six domains [3].

The Cochrane Handbook provides some examples of other potential threats to validity, such as design-specific risk of bias in non-randomized trials, baseline imbalance between groups of participants, blocked randomization in trials that are not blinded, differential diagnostic activity, study changes due to interim results, deviations from the study protocol, giving intervention before randomization, inappropriate administration of an intervention or having co-intervention(s), contamination due to drug pooling among participants, insufficient delivery of intervention, inappropriate inclusion criteria, using instruments that are not sensitive for specific outcomes, selective reporting of subgroups and fraud [3].

This list of potential other sources of bias mentioned in the Cochrane Handbook is limited, and it would, therefore, be useful to explore potential additional sources of 'other bias'. By consulting a more comprehensive list of potential other biases, the systematic review might recognize certain problems in included studies that might not otherwise consider a potential source of bias.

The aim of this study was to define which issues authors of Cochrane reviews describe as "other bias", to determine the prevalence of various categories of other bias and to quantify qualitative data which support the assessment of other bias.

Methods

We conducted a retrospective analysis of published Cochrane reviews.

Inclusion and exclusion criteria

We retrieved Cochrane reviews that included RCTs about interventions published from July 2015 to June 2016 ($N = 955$) by using Advanced search in The Cochrane Library. Diagnostic Cochrane reviews, empty reviews, overviews of systematic reviews and reviews withdrawn in this period were excluded. Cochrane reviews that included both RCTs and non-randomized trials were included, but only RoB of RCTs were analyzed.

Screening

One author assessed all titles/abstracts to establish the eligibility of Cochrane reviews for inclusion (LP). Another author verified all the assessments of the first author (AB). There were no disagreements.

Data extraction and categorization

Data extraction table was developed and piloted using five Cochrane reviews. Initially, one author manually extracted the data by copy-pasting from included Cochrane reviews and another author verified 10% of extractions. Of the 77 verified Cochrane reviews, we found 3 Cochrane reviews which were partially extracted (3.9%), which we consider to be a negligible percentage of the discrepancy. We extracted judgments (high, low or unclear risk) and supporting explanations for judgments (qualitative data which support the assessment to determine the reasons for the judgment) from the 'other bias' section of RoB table in Cochrane reviews. We also extracted judgments and support for judgments from additional non-standard domains (domains which are not covered by seven standard RoB domains in RoB table mentioned in the Background section) if Cochrane authors used them. For Cochrane reviews that did not use the 'other bias' domain in the RoB table or any other additional non-standard domains, we analyzed the text of results to see whether Cochrane authors mentioned any potential sources of other bias in the text of the review only. Each supporting explanations for judgments of risk of bias in the analyzed trials were categorized by two authors (AB and LP), via consensus. In 2018 we enlisted a help of information specialist who used software for data extraction, and compared manually extracted data with software-extracted data; we found 12 further discrepancies in extracted judgments.

Outcomes

We analyzed number, type, judgments and inconsistencies in judgments for certain comments about other risk of bias. These inconsistencies were judged as follows: we analyzed whether Cochrane authors used different RoB judgments for the same supporting comment. We quantified Cochrane reviews in which authors did not use 'other bias' domain for any of the included RCTs to determine whether they used some non-standard additional RoB domain instead of 'other bias'. We conducted a quantitative and qualitative analysis of these non-standard domains.

Statistics

We performed descriptive statistics using Microsoft Excel (Microsoft Inc., Redmond, WA, USA). We presented data as frequencies and percentages. In the primary analysis, we analyzed Cochrane reviews that had the 'other bias' domain in the RoB table. In the secondary analysis, we analyzed Cochrane reviews that did not have the 'other bias' domain or had different non-standard variations of RoB assessment that were not mentioned in the Cochrane Handbook.

Results

Primary analysis

We analyzed 768 Cochrane reviews that included 11,369 RCTs. Among those 768 Cochrane reviews, we included in the primary analysis 602 Cochrane reviews that had 'other bias' domain in the RoB tables. Those 602 Cochrane reviews included a total of 7811 RCTs. We analyzed 166 Cochrane reviews in the secondary analysis because they either did not have 'other bias' domain in RoB Tables ($N = 149$), or those Cochrane reviews had both 'other bias' domain and additional non-standard domains in the RoB Tables ($N = 17$). The flow diagram showing inclusion of Cochrane reviews is shown in Fig. 1.

Out of 602 Cochrane reviews in the primary analysis, there were 524 (87%) Cochrane reviews that described various sources of bias in the 'other bias' domain, while in 78 (13%) Cochrane reviews not a single source of other bias was reported. Furthermore, among 602

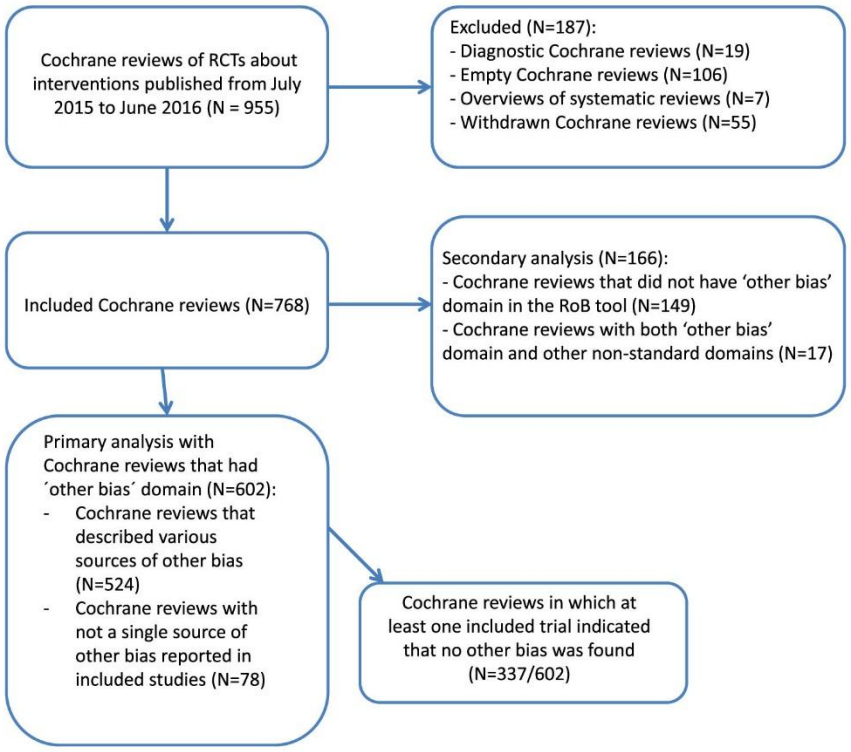

Fig. 1 Flow diagram presenting the inclusion of Cochrane systematic reviews in the study. We retrieved 955 Cochrane systematic reviews from the Cochrane Database of Systematic Reviews that were published from July 2015 to July 2016. We excluded 187 Cochrane reviews because they were either empty (without a single study included), diagnostic accuracy reviews, overviews of systematic reviews or they were withdrawn. We included 768 Cochrane reviews in our analysis; of those, 602 were included in our primary analysis because they had other bias domain in the Cochrane risk of bias tool, while 166 Cochrane reviews were included in our secondary analysis because they either did not have other bias domain in the Cochrane risk of bias tool, or they had this domain, but also other non-standard domains in the tool

Cochrane reviews from the primary analysis, there were 337 (56%) Cochrane reviews in which at least one included trial indicated that no other bias was found. Terminology for comments about non-existent other bias varied, even within individual Cochrane reviews. In 268 (80%) Cochrane reviews only one version of the comment that no other bias was found was used, while in 69 (20%) reviews Cochrane authors used different expressions in comments to indicate that no other sources of bias were found. Some examples of this varied terminology are shown in Additional file 1: Table S1.

In 40 (12%) out of 337 Cochrane reviews that indicated that no other bias was found, we observed discrepancies in judgment for this domain. Namely, Cochrane authors in these 40 Cochrane reviews sometimes indicated that lack of other bias was associated with low RoB, and sometimes they marked it as unclear or high RoB. In 59 (18%) of these 337 Cochrane reviews at least one support for judgment that indicated that no other bias was identified Cochrane authors judged as not being the low risk of bias (either high or unclear); in 278 Cochrane reviews this was judged as low RoB.

In 19 Cochrane reviews, all comments that referred to no other bias being identified were judged as unclear. In one review comment, 'no other bias' was judged as both low and high. References to Cochrane reviews for these specific examples are in Additional file 2: Table S2. In one review the same comment was judged in different RCTs as either low or high. In one review the same comment was judged in different RCTs as either low or unclear or high.

Of the 7811 trials that were included in the 602 Cochrane reviews from the main analysis, in 3703 (47%) trials domain for other bias indicated in the support for judgment that other bias was not identified. Of those 3703 trials, there were 288 (7.8%) that were judged as unclear RoB, 4 (0.1%) that were judged as high RoB, while the others ($N = 3411$, 92.1%) were judged as low RoB.

Sources of other bias

In the 524 analyzed Cochrane reviews that described various sources of other bias, there were 5762 different supporting explanations for judgments of other bias that we categorized into 31 categories. In 535 trials it was indicated only that it was not possible to assess other bias. For 24 (4%) of those 535 trials it was not indicated why this was not possible, while the most common reasons for not being able to assess other bias were that there was 'insufficient information' ($N = 392$, 73%), the trial was published as a conference abstract only ($N = 78$, 15%) and that the trial was published in a foreign language so there were issues with translation ($N = 11$, 2%). Cochrane authors were not consistent in judging this type of supporting explanation; for 11 (2%) trials it was judged as high RoB, for 520 (94%) as unclear RoB and for 4 (0.7%) as low RoB.

There were 236 trials for which Cochrane authors simply wrote that issues related to other bias were not described or unclear. This type of supporting explanation was also inconsistently judged by the Cochrane authors; 7 (3%) judged it as low RoB and 229 (97%) as unclear RoB.

The remaining 4991 explanations for judgments of other bias were divided into 29 categories that are shown in Table 1. The most frequently used categories of explanations for other bias were related to baseline characteristics of participants, funding of a trial, reporting, sample size and conflict of interest (Table 2). Cochrane authors used the domain for other bias to indicate positive, negative and unclear aspects of a trial. For example, three most common types of explanations in the category related to baseline characteristic

Table 1 Different categories of other bias (based on 4991 explanations) in Cochrane systematic reviews

Category	N (%)
Baseline characteristics of participants	1067 (21.4)
Funding	774 (15.6)
Sample size	405 (8.1)
Reporting	381 (7.6)
Conflict of interest	288 (5.8)
Inclusion and exclusion criteria	197 (3.9)
Confounding	196 (3.9)
Analyses	191 (3.8)
Outcome domains and outcome measures	135 (2.7)
Co-interventions	134 (2.7)
Deviations from the protocol	123 (2.5)
Randomisation	111 (2.2)
Terminated early	108 (2.2)
Issues related to cross-over trials	98 (2)
Intention-to-treat analysis (ITT)	95 (1.9)
Study design	76 (1.6)
Compliance	72 (1.4)
Attrition	71 (1.4)
Contamination	65 (1.3)
Follow-up and study duration	46 (0.9)
Blinding	25 (0.5)
Clustering	17 (0.3)
Selection bias	17 (0.3)
Protocol registration	16 (0.3)
Study quality	9 (0.2)
Publication bias	7 (0.1)
Adequacy of comparators	5 (0.1)
Inexplicable	85 (1.7)
Other	177 (3.6)

Table 2 Judgments for the 20 most common explanations of other bias

Explanation	Total	High, N (%); n[a]	Unclear, N (%); n[a]	Low, N (%); n[a]
Not possible to assess other bias	504	7 (1.4);*7*	494 (98);*117*	3 (0.6);*3*
Baseline characteristics similar between the groups	314	0 (0);*0*	24 (8);*13*	290 (92);*61*
Not described/unclear	233	0 (0);*0*	226 (97);*54*	7 (3);*4*
Baseline imbalance between groups of participants	167	91 (54);*56*	62 (37);*41*	14 (9);*12*
Funding: industry	162	83 (51);*28*	77 (48);*25*	2 (1);*2*
Potential confounding factors	120	63 (53);*38*	47 (39);*34*	10 (8);*9*
Not enough information on baseline characteristics of participants	88	8 (9);*6*	78 (89);*39*	2 (2);*2*
Funding: non-profit	86	0 (0);*0*	4 (5);*4*	82 (95);*33*
Funding: not reported	72	0 (0);*0*	68 (94);*15*	4 (6);*4*
Important parameters not reported	61	19 (31);*14*	41 (68);*28*	1 (1);*1*
Sample size: calculation of sample size not provided	42	24 (57);*6*	17 (41);*7*	1 (2);*1*
Potential randomisation problem	40	9 (23);*9*	28 (70);*13*	3 (7);*3*
Potential problem with inclusion criteria	40	16 (40);*15*	22 (55);*12*	2 (5);*2*
Deviations from the study protocol	37	16 (43) *13*	18 (49) *15*	3 (8) *3*
No relevant subgroup analysis	36	10 (28);*1*	26 (72);*1*	0 (0);*0*
Funding: intervention supplied by industry	32	14 (44);*7*	12 (38);*10*	6 (18);*3*
Adequate	28	0 (0);*0*	0 (0);*0*	28 (100);*1*
No information on the validity of the outcome measure	27	3 (11);*3*	23 (85);*5*	1 (4);*1*
Sample size: performed calculation	24	1 (4);*1*	3 (12);*3*	20 (84);*9*
Sample size: small	23	8 (35);*5*	15 (65);*5*	0 (0);*0*

[a]*n* = Number of Cochrane reviews that included at least one RCT with this characteristic

of participants indicated that either baseline characteristics were similar, or that there was the imbalance in baseline characteristics, or that there was insufficient information about it (Additional file 3: Table S3). Among 4991 explanations, we were unable to categorize 85 of them because they were uninformative, including explanations such as 'Adequate' or 'N/A' or 'Other risk of bias was possible'. Finally, there were 112 explanations that were used only once or twice in RoB tables we analyzed so we categorized that group as 'Other explanations'. A table with all the types of explanations is presented in Additional file 3: Table S3.

Partial studies included in the primary analysis

We found 34 Cochrane reviews with specific partial data regarding other bias, i.e. whose 'other bias' domains in RoB tables were not complete. We divided them into four distinct groups: the first group with 28 reviews that had judgments for 'other bias', but not all had accompanying comments, second group with 4 reviews where only one included RCT did not have the 'other bias' domain, third group with one review with included RCT without 'other bias' domain and included RCT with only judgment without comment, and fourth group with one review where RoB table was completely missing for 6 included RCTs. References to Cochrane reviews and RCTs for these specific examples are in Additional file 2: Table S2. Some Cochrane reviews had additional non-standard RoB domains, separately or in addition to the 'other bias' domain. Categories of additional non-standard RoB domains in Cochrane reviews are shown in Table 3.

Cochrane authors' judgments of different explanations for 'other bias'

There were 3033 trials for which only one category of explanation was written by Cochrane authors. When the explanation had only one category of comment we could be certain that the judgment referred only to that specific comment so we analyzed those in detail to see how the Cochrane authors judge different explanatory comments. There were 259 types of different explanations among those 3033 trials. We analyzed in more detail those judgments for 20 most common explanations of other bias and found very high inconsistency in how Cochrane authors judge the same explanations (Table 2).

Secondary analysis

Reviews without 'other bias' domain in the RoB table

Among 149 Cochrane reviews that did not have 'other bias' domain in the RoB table, there were 102 reviews that did not have any other replacement domain for 'other bias'. These 102 reviews used the varied number of standard RoB domains. In those 102 reviews, the number of

Table 3 Categories of additional non-standard RoB domains in Cochrane systematic reviews

Additional category	N of Cochrane reviews
Group similarity at baseline (selection bias)	11
Baseline data	5
Baseline outcome measures (similar)	3
Groups balanced at baseline/ balance in baseline characteristics	2
Baseline characteristics of participants	1
Baseline comparability of treatment and control groups	1
Baseline measures	1
Similarity of baseline characteristics[a]	1
Treatment/control groups comparative at entry	1
Major imbalance in important baseline confounders	1
Comparability of groups on different prognostic characteristics[a]	1
Size	8
Size of the study	5
Small sample size bias	4
Sample size[a]	2
Sufficient sample size[a]	1
Power calculation[a]	1
Timing of outcome assessment (similar)[a]	10
Adequate follow-up	2
Study duration	2
Early stopping	1
Groups received comparable treatment	2
Care program identical/ identical care	2
Treatment fidelity[a]	1
Free of systematic differences in care?[a]	1
Consistency in intervention delivery	1
Equality of treatment	1
Protocol deviation balanced	1
Groups received same intervention	1
Compliance/adherence assessed (acceptable)	7
Compliance with recommendation reliable?	1
Compliance acceptable[a]	1
Source of funding/ sponsorship	4
For profit funding[a]	1
Funding[a]	1
Vested interest bias	1
Conflict of interest	1
Co-intervention avoided or similar[a]	5
Co-interventions	2
Groups received same co- interventions	1
Intention to treat	5
Incorrect analysis	1
Results based on data dredging?	1
Analyses adjust for different lengths of follow-up workers?	1
Appropriate statistical tests use?	1
Adequate adjustment for confounding in the analyses?	1
Contamination/ protection against contamination	3
Validity of outcome measures	1
Reliability of outcome measures	1
Outcome measures used valid and reliable?	1
Free from performance bias	1
Performance bias as «differential expertise» bias	1
Performance bias as comparability in the experience of care providers	1
Adequate patient description	1
Recruitment of participants from the same population?	1
Recruitment of participants over the same study period?	1
Washout/ carry-over effect in cross-over study designs	2
Overall assessment of bias risk	1
Summary of risk of bias for Consumption outcome	1
Researcher allegiance[a]	1
Therapist allegiance[a]	1
CHBG (Cochrane hepato-biliary group) combined assessment (mortality)[a]	1
CHBG combined assessment (hepatic encephalopathy)[a]	1
Comparability with individually randomized trials	1
Detection bias (biochemical validation of smoking outcomes)	1
Ethical approval	1
Explicit inclusion/exclusion criteria	1
Free of dietary differences other than fat?[a]	1
Loss of clusters	1
Methods for selecting cases to adjudicate	1
Outcome description	1
Publication format	1
Recruitment bias	1

[a]domains found in 9 Cochrane reviews that had both 'other bias' domain and additional non-standard domain(s) for other bias in RoB tables

standard RoB domains that were used varied, with one standard RoB domain in 4 reviews, three RoB domains in 7 reviews, four RoB domains in 15 reviews, five domains in 51 reviews and 6 domains in 25 reviews.

For this group of Cochrane reviews, that did not have the 'other bias' domain in the RoB table, we analyzed texts of results to see whether they mentioned any other sources of bias, beyond the standard six domains, in the section 'Risk of bias in included studies'. We found that 68/102 (67%) did not mention any sources of other bias in the results of the review. However, the remaining 34 (33%) did have comments about the other bias. Three of those 34 stated that they had not found any other risk of bias, while 31 reviews out of those 34 reported in the text of results that the included studies had had from 1 to 6 different categories of other bias.

Reviews with both 'other bias' domain and additional non-standard domain(s) for other bias in RoB tables

Nine Cochrane reviews had both 'other bias' domain and additional non-standard domain(s) for other bias in RoB tables (References in Additional file 2: Table S2). Those reviews used from 1 to 4 additional non-standard domains; 18 in total. Those additional non-standard RoB domains are listed in Table 3 and marked with the asterisk.

Reviews without 'other bias' domain but with the additional non-standard domain(s)

There were 57 Cochrane reviews that did not have the 'other bias' domain, but they did have additional non-standard RoB domains apart from the standard domains in the Cochrane RoB table. Most of the reviews had only one additional non-standard domain ($N = 24$), while others had 2–8 additional domains per each RCT. Table 3 shows non-standard domains that were used in those reviews without 'other bias' domain.

Reviews that consistently did not use support for judgment or they used non-standard judgments

We found 9 Cochrane reviews that consistently did not use supporting explanations for judgment or they used non-standard judgments. In 5 reviews authors used judgments low, high or unclear RoB, but without comments as support for judgment. In one review all trials were marked with the unclear risk of other bias without any comment as support for judgment. In four reviews all trials were marked with low risk of other bias without any comment as support for judgment. We also found 4 reviews that did not have judgments low-high-unclear, but different kinds of judgments. One review had judgments yes/no without supporting comments; two reviews had judgments yes, no or unclear, with supporting comments and there was one review with judgments A-adequate and B-unclear (References in Additional file 2: Table S2).

Discussion

In this study, we analyzed 768 Cochrane systematic reviews, with 11,369 included trials. We found that Cochrane authors used numerous different categories of sources of other bias and that they were not judging them consistently. We categorized different types of supporting explanations into 31 categories, and we found numerous other inconsistencies in reporting of sources of other bias in Cochrane reviews. Findings of this study are disconcerting because consistency in secondary research is very important to ensure comparability of studies.

Insufficient and unclear reporting of the 'other bias' domain was very common in the Cochrane reviews we analyzed. Among the most common support for judgment were comments that we categorized as 'not described/unclear', which is puzzling because 'other bias' domain is not specific like the other six domains of the RoB tool, and it is, therefore, difficult to fathom what it means that other bias was not described or that it was unclear. If the authors did not find sources of other bias, or if they thought that they could not assess other bias because of the brevity of report or language issues, they should have stated that. Likewise, for some trials, the only supporting explanation was that other bias was 'Adequate'. Without any further explanations, readers cannot know what exactly the Cochrane authors found to be adequate in terms of other potential sources of bias. Many systematic reviews had a high number of included studies, and therefore some comments were repeated multiple times in the same systematic review.

The most commonly used specific category of other bias referred to baseline characteristics of participants. In RCTs, randomization should ensure allocation of participants into groups that differ only in intervention they received. Randomization should ensure that the characteristics of participants that may influence the outcome will be distributed equally across trial arms so that any difference in outcomes can be assumed to be a consequence of intervention [4]. Baseline imbalances between the groups may indicate that there was something wrong with the randomization process, or that they might be due to chance [5]. Severe baseline imbalances can occur because of deliberate actions of trialists if they aim to intentionally subvert the randomization process [6] or due to unintentional errors.

Chance imbalances should not be considered a source of bias, but it may be difficult to distinguish whether baseline imbalances are caused by chance or intentional actions. If there are multiple studies included in a meta-analysis, it could be expected that chance imbalances will act in opposite directions. But the problem may occur if there is a pattern of imbalances across several trials that may favor one intervention over another, suggesting imbalance due to bias and not due to chance

[7]. Cochrane is now developing a second generation of the RoB tool, titled RoB 2.0, and one of the signaling questions in the RoB domain about randomization process asks "Were there baseline imbalances that suggest a problem with the randomization process" [7]. The fact that so many Cochrane authors used comments about baseline imbalance as a domain of other bias, and not in the RoB domain about random sequence generation (selection bias) indicate that many Cochrane authors consider that this aspect should be emphasized separately from the selection bias domain.

The second most commonly used category of supporting explanations was related to funding of a trial, and comments about conflicts of interest were the fifth most common category. This is in direct contrast with the recommendations from the Cochrane Handbook, where it is acknowledged that information about vested interests should be collected and presented when relevant, but not in the RoB table; such information should be reported in the table called 'Characteristics of included studies' [8]. RoB table should be used to describe specific methodological aspects that may have been influenced by the vested interest and directly lead to RoB [8]. Therefore, it is obvious that the authors of the Cochrane Handbook assume that the influence of sponsors can be mediated via other domains of RoB tool such as selective reporting of favorable outcomes.

However, Lundh et al. have published a Cochrane review in 2017 about industry sponsorship and research outcomes, in which they included 75 primary studies, which shows that commercial funding leads to more favorable efficacy results and conclusions compared to non-profit funding [9]. They concluded that industry sponsorship introduces bias that cannot be explained by standard domains of Cochrane's RoB assessment [9]. The debate about whether funding presents the source of bias or not is ongoing in the Cochrane, with some considering that commercial funding is a clear risk of bias, while others argue against such standpoint [10, 11]. This debate apparently reflects the current situation in which many Cochrane authors continue to use funding and conflict of interest as a source of other bias despite the official warning against such use of information about sponsorship from the Cochrane Handbook, as we have demonstrated in this study.

The third most frequent category of supporting explanations for other bias was related to poor reporting, where Cochrane authors indicated that relevant information was missing or were inadequately reported. Poor reporting hinders transparency, as it allows authors to avoid attention to weak aspects of their studies. For this reason, reporting guidelines should be used [12].

Comments about sample size were the fourth most common category either in a sense that the trial did or did not report sample size calculation, or that sample size was "small" without any further explanation of what the Cochrane authors considered to be a small sample. There were 21 trials for which Cochrane authors wrote that there were fewer than 50 participants in each arm. It is unclear where this cut-off is coming from, as there is no such guidance in the Cochrane Handbook in the chapter about the risk of bias. On the contrary, chapter 8.15.2. of the Cochrane Handbook specifically warns that "sample size or use of a sample size (or power) calculation" are examples of quality indicators that "should not be assessed within this domain" [8].

The Cochrane Handbook also warns that authors should avoid double-counting, by not including potential sources of bias in the 'other bias' domain if they can be more appropriately covered by other domains in the tool [8]. As can be seen by our study, Cochrane authors sometimes do double-counting because there were categories of comments supporting judgments that could have been addressed in the first six domains.

As we have shown, most Cochrane authors decided to use the other bias domain to describe potential additional biases that were not covered in the first six domains of the RoB tool. In the proposed RoB tool 2.0 there is no 'other bias' domain [7]. The proposed RoB tool is much more complex, compared to the current version of the RoB tool, and many items that were specifically emphasized by Cochrane authors in the other bias domain, as shown in our study, are addressed in the RoB 2.0 tool. However, there are still potential biases from other sources that the RoB 2.0 may neglect by omitting the RoB domain for other bias. Relevant other bias that were identified in our study include, for example, problems with inclusion and exclusion criteria, data analyses, outcome domains and outcome measures that were used, usage of co-interventions that are not accounted for, deviations from the protocol, study design, issues related to specific types of trials such as cross-over trials and biases specific to other to certain topics. Therefore, we believe that there is a rationale for including 'other bias' domain in revised RoB tool too.

We have already conducted a similar analysis of Cochrane RoB domain related to other RoB domains, and we found that judgments and supports for judgments in those domains were very inconsistent in Cochrane reviews [13–15]. This analysis related to sources of other bias in Cochrane reviews contributes to the perception that Cochrane RoB tool is inconsistently used among Cochrane authors. The authors do not necessarily follow guidance from the Cochrane Handbook. In the support for judgment, they mention issues that the Cochrane Handbook explicitly warns against. Various comments that serve as supports for judgments were inconsistently judged across Cochrane reviews and trials included in those reviews. Cochrane authors also use inconsistent terminology to describe the same concepts. Increasing complexity of the RoB tool, as proposed in the

RoB tool 2.0 will likely only increase this problem of insufficient consistency in RoB appraisal and worsen this problem of insufficient comparability of judgments of RoB across Cochrane reviews.

Furthermore, our study indicated that Cochrane authors extensively use the available option to customize the RoB table. We found that there were as many as 102 (13%) out of 768 analyzed Cochrane reviews that did not use the other bias domain in the RoB table at all. Cochrane reviews are produced using the software Review Manager (RevMan). As soon as an author inserts a new study in the RevMan among included studies, an empty RoB table for the study automatically appears, with seven pre-determined domains. Therefore, Cochrane authors need to intentionally remove or add some domains if they want to customize the RoB table. Among 102 Cochrane reviews that did not have other bias domain, 33% of those reviews had comments about other potential sources of bias in the body of the manuscript. It is unclear why some Cochrane authors use only text for comments about other bias instead of using RoB table for this purpose. Additionally, we observed that in many Cochrane reviews without other bias domain there were other customizations of the RoB table, which had from one to six other, standard RoB domains included. Exactly half of those reviews without other bias domain in the RoB table had less than six standard domains in the RoB table.

Results of this study can contribute to better reporting of future systematic reviews and help authors of systematic reviews to avoid mistakes. Firstly, results of this manuscript will provide more comprehensive information for Cochrane authors regarding 'other bias' domain – we present many sources of other bias that Cochrane authors recognize, and that are not mentioned in the Cochrane Handbook. Secondly, we showed mistakes that Cochrane authors are doing when they mention in 'other bias' domain issues that actually belong to other six domains of Cochrane RoB tool. Thirdly, we are also pointing out mistakes that Cochrane authors are doing despite explicit instructions from the Handbook, i.e. authors use sample size and funding to comment about potential bias, even though the Handbook explicitly warns against this. Although our study was focused only on Cochrane reviews, our results are relevant also for non-Cochrane reviews that use Cochrane's risk of bias tool. Therefore, our manuscript can help authors of Cochrane and non-Cochrane reviews to create better and more consistent reviews, to recognize additional potential sources of bias in trials they analyze, and to avoid mistakes that we have observed.

Limitation of our study is that we included in our analysis a limited number of analyzed Cochrane reviews, which were published in 2015 and 2016. We chose this convenience sample of Cochrane reviews because we were interested in the state of the 'other bias' domain in recent times; we did not aim to analyze the change of this domain over the very long time period. However, considering the number of Cochrane reviews analyzed, and the number of inconsistencies we observed, we have no reason to suspect that the results would be significantly different if a bigger cohort of published Cochrane reviews would have been used. It takes a long time to manually extract, check, analyze and categorize more than ten thousands of RoB domains, and therefore using the same methodology on a larger sample might not be feasible. It is possible that some unintentional errors in categorizations may have been made, and therefore, for transparency, we decided to present all categories and sub-categories of the supporting explanations we encountered in the Additional files 1, 2 and 3. Additionally, all systematic reviews are not the same and our findings cannot be generalized to all systematic reviews – we analyzed only Cochrane systematic reviews of RCTs because Cochrane RoB tool was developed for these types of studies. However, we believe that our findings can be very useful also for authors of non-Cochrane reviews who will use Cochrane RoB tool in their methodology.

Finally, it is worth emphasizing that it is possible that some trials from our cohort were included in more than one review, and that Cochrane authors could give them different judgments for 'other bias'. It has been shown before that authors of different reviews can make different RoB judgments of the same trials [16]. However, such analysis was not the aim of our study.

Conclusion

Cochrane authors mention a wide range of sources of other bias in the RoB tool and they inconsistently judge the same supporting explanations. Inconsistency in appraising risk of other bias hinders reliability and comparability of Cochrane systematic reviews. Discrepant and erroneous judgments of bias in evidence synthesis may hinder implementation of evidence in routine clinical practice and reduce confidence of practitioners in otherwise trustworthy sources of information. These results can help authors of Cochrane and non-Cochrane reviews to gain insight into various sources of other bias that can be found in trials, and also to help them avoid mistakes that were recognized in published Cochrane reviews. Potential remedies include more attention to author training, better resources for Cochrane authors, better peer-review and editorial consistency in the production of Cochrane systematic reviews.

Additional files

Additional file 1: Table S1. Some examples of different versions of support for judgment indicating that no other bias was found. In 268 (80%) Cochrane reviews only one version of the comment that no other bias was found was used, while in 69 (20%) reviews Cochrane authors used different expressions in comments to indicate that no other sources

of bias were found. Some examples of this varied terminology are shown in Table S1. (DOCX 13 kb)

Additional file 2: Table S2. Cochrane systematic reviews and randomized controlled trials specifically mentioned in the results as those that had different judgment for having no bias, partial information about other bias, or were included in secondary analyses. In 19 Cochrane reviews, all comments that referred to no other bias being identified were judged as unclear. In one review comment, 'no other bias' was judged as both low and high. References to Cochrane reviews for these specific examples are shown in this Additional file. (DOCX 87 kb)

Additional file 3: Table S3. Categories of explanations of other bias in analyzed Cochrane risk of bias tables. In the 524 analyzed Cochrane reviews that described various sources of other bias, there were 5762 different supporting explanations for judgments of other bias that we categorized into 31 categories. The main text describes the most common categories of explanations, while all the types of explanations is presented in Table S3. (XLSX 37 kb)

Abbreviations
RCT: Randomized controlled trial; RCTs: Randomized controlled trials; RoB: Risk of bias

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions
Study design: LP. Data analysis and interpretation: AB, AP, LB, YG, MARP, TPP, LP. Drafting the first version of the manuscript: AB, LP. Revisions of the manuscript: AB, AP, LB, YG, MARP, TPP, LP. All authors read and approved the final manuscript. All authors agree to be accountable for this work.

Ethics approval and consent to participate
Not applicable; in this study we analyzed only published manuscripts.

Consent for publication
Not applicable.

Competing interests
Tina Poklepovic Pericic is a volunteer co-director of Cochrane Croatia. Livia Puljak and Andrija Babic are volunteer members of Cochrane Croatia. Livia Puljak is a Section Editor at the BMC Medical Research Methodology, but she was not involved in any way with editorial handling of this manuscript. Other authors have no competing interests to declare.

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Author details
[1]Institute of Emergency Medicine in Split-Dalmatia County, Split, Croatia. [2]Medical student, University of Split School of Medicine, Split, Croatia. [3]Faculty of Medicine and Dentistry, Palacký University Olomouc, Olomouc, Czech Republic. [4]Medical University of Plovdiv, Plovdiv, Bulgaria. [5]Faculty of Health Sciences - University of Beira Interior, Covilhã, Portugal. [6]Catholic University of Croatia, Zagreb, Croatia.

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ORIGINAL ARTICLE

Overall bias methods and their use in sensitivity analysis of Cochrane reviews were not consistent

Andrija Babic[a], Ivana Vuka[b], Frano Saric[c], Ivona Proloscic[d], Ema Slapnicar[d], Jakica Cavar[e], Tina Poklepovic Pericic[f], Dawid Pieper[g], Livia Puljak[h,*]

[a]*Institute of Emergency Medicine in Split-Dalmatia County, Split, Croatia*
[b]*Laboratory for Pain Research, Department of Anatomy, Histology and Embryology, University of Split School of Medicine, Split, Croatia*
[c]*Department of Radiology, University Hospital Split, Split, Croatia*
[d]*University of Split School of Medicine, Split, Croatia*
[e]*Department of Neuroscience, University of Lethbridge, Lethbridge, Canada*
[f]*Department of Research in Biomedicine and Health, University of Split School of Medicine, Split, Croatia*
[g]*Faculty of Health, School of Medicine, Institute for Research in Operative Medicine, Faculty of Health, School of Medicine, Witten/Herdecke University, Cologne, Germany*
[h]*Center for Evidence-Based Medicine and Health Care, Catholic University of Croatia, Zagreb, Croatia*

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Abstract

Objective: The objective of the study was to analyze methods of assessing "overall bias" in Cochrane reviews of interventions published in the Cochrane Database of Systematic Reviews and sensitivity analyses related to overall risk of bias (RoB).

Study Design and Setting: From Cochrane reviews published within 3 years, from July 2015 to June 2018, we extracted data regarding methods of judging overall bias for a single trial, as well as details regarding methods used in frequency of RoB in sensitivity analyses.

Results: Of the 1,452 analyzed Cochrane reviews, 409 mentioned assessment of overall RoB on a study level. In 107 reviews, authors clearly specified key domains that determined the overall RoB, whereas in the remaining reviews, assessment of overall bias was not in line with the Cochrane Handbook. Among 268 Cochrane reviews that had any RoB-related sensitivity analysis, in 56 (21%) reviews, the authors reported a significant change for at least one outcome compared with the initial analysis.

Conclusion: Highly heterogeneous approaches to summarizing overall RoB on a study level and using RoB for sensitivity analyses may yield inconsistent and incomparable results across Cochrane reviews.

Keywords: Systematic review; Cochrane; Risk of bias; Overall bias; Sensitivity analysis; Methodology

1. Introduction

Cochrane advocates rigorous methodological standards and therefore Cochrane systematic reviews are considered the gold standard when it comes to the synthesis of evidence [1]. An important part of the systematic review methodology is an appraisal of the risk of bias (RoB) in included studies. The potential effect of bias is that trialists will reach wrong conclusions about efficacy and safety of studied interventions [2].

In Cochrane systematic reviews, RoB of each included individual study is appraised using Cochrane RoB tool, which has seven domains. Cochrane authors report RoB assessment in a table, whereas they provide a judgment whether there is a "low risk," "high risk," or "unclear risk" of bias for each domain, and each judgment needs to be supported by the accompanying comment, which gives rationale for the judgment [3].

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* Corresponding author: Center for Evidence-Based Medicine and Health Care, Catholic University of Croatia, Ilica 242, 10000 Zagreb, Croatia. Tel.: +385-1-370-6600; fax: +385-1-370-6601.

E-mail addresses: livia.puljak@gmail.com; livia.puljak@unicath.hr (L. Puljak).

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What is new?

Key findings

- The minority of analyzed Cochrane reviews mentioned overall risk of bias (RoB) assessment, but only a quarter of them did it in line with recommendations from the Cochrane Handbook.
- The majority of analyzed Cochrane reviews planned sensitivity analysis to explore the effect of RoB/quality of included trials on results, but only one-fifth of those reviews actually reported that they made such analysis mostly because there were few high-quality trials with "low" RoB.
- Among Cochrane reviews that made sensitivity analysis to explore the effect of RoB/quality of included trials on results in the two-thirds, the authors reported there were no differences between the primary analyses based on the RoB, in one-third of reviews, the authors reported change in effect for at least one outcome, whereas in 21%, it was significant change.

What this adds to what was known?

- Multiple studies have shown that Cochrane reviews suffer from a high prevalence of inconsistencies related to RoB assessment, and it was already published that majority of Cochrane reviews planned sensitivity analysis to explore the effect of RoB/quality of included trials on results, but only small number of them actually reported that they made such analysis. Highly heterogeneous approaches to summarizing overall RoB on a study level and using RoB for sensitivity analyses may yield inconsistent and incomparable results across Cochrane reviews

What is the implication and what should change now?

- Interventions for ensuring consistent use of systematic review methodology in Cochrane reviews process would be welcome and very relevant for practice and research, which rely on their conclusions for the advancement of medicine and future research.

Authors of systematic reviews may consider making a summary assessment of RoB at a study level. However, The Cochrane Handbook Version 5.1.0 that was applied to reviews from investigated period indicates that summarizing the overall RoB in a review should be avoided because it requires value judgments about which outcomes are critical to a decision, and judgments about which outcomes are critical to a decision may vary from setting to setting. The Handbook states that "*summary assessment of the risk of bias across all outcomes for a study is generally of little interest*", while it also comes with the challenge that the overall RoB might be different for different outcomes [4].

However, it has been reported that Cochrane review authors sometimes assess overall RoB and conduct sensitivity analysis based on such assessment [5]. The idea of an overall RoB is to facilitate decision making, and an overall RoB judgment was included in new tools for assessing RoB in systematic reviews [6] and nonrandomized studies about efficacy of interventions [7].

The aim of this study was to analyze definitions of "overall bias" in Cochrane reviews of interventions published within 3 years in the Cochrane Database of Systematic Reviews, as well as method and frequency of using the RoB in sensitivity analyses.

2. Methods

2.1. Study design

We conducted a primary methodological study in which unit of analysis was a published Cochrane systematic review and extracted data regarding overall RoB on a study level. Hereby we defined overall RoB on a study level as RoB assessment of an entire RCT as having an overall high, low, or unclear RoB, that is, Cochrane authors aiming to provide a single RoB judgment for an entire study, in addition to the judgment for each domain in a Cochrane RoB tool. When Cochrane authors used expression "overall RoB" to simply indicate that they have shown summarized RoB across studies and across RoB domains in customary RoB figures in a Cochrane review, we did not extract such information, as that kind of data presentation does not correspond to a concept of overall RoB within a study.

2.2. Search strategy and eligibility criteria

We analyzed Cochrane reviews of interventions, both new and updates, published from July 2015 to June 2018 (details about the search are presented in Supplementary File 1). Diagnostic Cochrane reviews, empty Cochrane reviews, overviews of systematic reviews, and Cochrane reviews withdrawn in this period were excluded. Protocols for Cochrane reviews were also excluded.

2.3. Screening for eligible reviews

Two authors (A.B. and L.P.) independently analyzed all titles/abstracts to check for eligibility of Cochrane reviews for inclusion. When necessary, discrepancies in judgment were planned to be resolved by the third author (T.P.P.); however, there were no discrepancies.

2.4. Data extraction

A data extraction table was developed a priori and piloted using five Cochrane systematic reviews that are

Table 1. Cochrane reviews that mentioned assessment of overall RoB on the study level

Group	*N* (%)
Cochrane reviews which simply indicated that the overall risk of bias on a study level was assessed based on the criteria from the Cochrane Handbook Example of such wording is: "*We made explicit judgments about whether the RCTs were at high risk of bias, according to the criteria given in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011)*"	131 (32)
Cochrane reviews in which any domain could contribute to overall RoB assessment Example of such wording is: *"We categorised the overall risk of bias of individual studies as being at low, high, or unclear risk of bias according to the following criteria.* • *Low risk of bias (plausible bias unlikely to seriously alter the results) if all domains were at low risk of bias.* • *High risk of bias (plausible bias that seriously weakens confidence in the results) if one or more domains were at high risk of bias* • *Unclear risk of bias (plausible bias that raises some doubt about the results) if one or more domains were at unclear risk of bias"*	125 (30.6)
Cochrane reviews which clearly specified key domains that determined the overall RoB Example of such wording is: *"We considered random sequence generation, allocation concealment, selective outcome reporting, and incomplete outcome data to be key domains. We judged a study to have a high overall risk of bias when we judged one or more key domains to have a high risk of bias*"	107 (26.2)
Cochrane reviews with various numerical indicators regarding the overall RoB Example of such wording is: *"We therefore used the Cochrane "Risk of bias" tool and assessed the risk of bias of each individual study. We considered studies at "moderate" risk of bias if we found more than two items to be at "high" risk or "unclear" risk. We considered studies at "low" risk of bias if we scored fewer than two items as having "high" risk or "unclear" risk in the "Risk of bias' summary"*	22 (5.4)
Cochrane reviews in which it was indicated that they used key domains for determining overall RoB on the study level, but did not provide information which key domains those were Example of such wording is: *"We judged each criterion for bias on a three-point scale 'low risk,' 'high risk,' and 'unclear risk' (Higgins 2011), and constructed a 'Risk of bias' table. 'Low risk,' when there was a low risk of bias across all key domains. 'Unclear risk,' when there was an unclear risk of bias in one or more of the key domains. 'High risk,' when there was a high risk of bias in one or more of the key domains"*	17 (4.2)
Cochrane reviews that used overall RoB assessments specific for Cochrane Back and Neck group	4 (1)
Cochrane reviews which had included overall RoB assessment on study level in the Cochrane RoB table	2[a] (0.4)
Cochrane review that indicated "We made an evaluation of the overall risk of bias, based on the relative importance of the various domains listed"	1 (0.2)
Total	409 (100)

Abbreviation: RoB, risk of bias.
[a] One review [9] had two domains for "overall bias" in RoB table—one for nonmortality outcomes and one for mortality.

included in the analysis. Five authors (I.V., F.S., I.P., E.S., and J.C.) participated in initial data extraction in a way that all data were extracted by one author independently; in the second phase, three authors (A.B., T.P.P., and L.P.) verified all extracted data independently.

The following data were collected: (1) Cochrane review group; (2) is there a definition of overall bias? If yes, the definition was extracted; (3) did the authors write in the review methods that they planned to conduct sensitivity analysis based on the RoB or quality? If yes, the definition was extracted from methods, but we reported separately whether the authors had defined what did they considered "quality" in that context; (4) did the authors actually conduct this type of sensitivity analysis for quality?; (5) did the authors include "overall bias" as a domain in the RoB table? We have checked all parts of reviews, including "differences in protocol and review" section.

2.5. Data synthesis

We grouped data for methods regarding overall RoB into multiple categories that were not defined a priori; instead, we analyzed our findings and reached consensus within the team about categories that would best describe our findings. For all extracted data, descriptive statistics were conducted, using frequencies and percentages. Microsoft Excel (Microsoft Corp., Redmond, WA, USA) was used for generating descriptive statistics.

3. Results

3.1. Methods for assessing overall risk of bias in Cochrane reviews

We analyzed 1,452 Cochrane reviews (list of analyzed reviews is available in Supplementary File 2). There were 28% ($N = 409$) Cochrane reviews that mentioned assessment of overall RoB on the study level; 389 in the methods and 20 in other parts of the review. We divided them into 8 groups (Table 1).

Most commonly, in 131 (32%) Cochrane reviews, authors simply indicated that the overall RoB on a study level was assessed based on the criteria from the Cochrane Handbook, without any further details. However, none of those

131 Cochrane reviews actually had reported in their results overall RoB assessment on a study level, and the only mention of the overall RoB on a study level remained in the methods. In 125 (31%) reviews, any domain could contribute to overall RoB (see example in Table 1).

In the third common category of overall RoB assessment on a study level, there were 107 (26%) reviews where authors clearly specified key domains that determined the overall RoB. Prevalence of those key domains is shown in Table 2. Thirteen of those 107 reviews included nonstandard RoB items in the overall RoB assessment (Table 2).

In one category, there were four reviews that used overall RoB assessments specific for Cochrane Back and Neck group; these reviews used 12 RoB criteria, whereas they labeled the RoB for a trial either as "low risk" (at least six of the 12 criteria met) or as "high risk" (fewer than six criteria met).

Finally, there was one Cochrane review that indicated "We made an evaluation of the overall RoB, based on the relative importance of the various domains listed," but without any further details about the relative importance of RoB domains.

3.2. Planning sensitivity analysis based on risk of bias

Of 1,452 included Cochrane reviews, there were 958 (66%) reviews that reported they had planned to conduct at least one sensitivity analysis to explore the effect of RoB or trial quality. In 336 (23%) Cochrane reviews such sensitivity analysis was not mentioned. For 158 (11%) Cochrane reviews, it was not possible to determine whether or not they had planned any sensitivity analysis based on RoB because authors did not report what kind of sensitivity analysis they had planned or could not do (Figure 1). For example, they simply wrote "*Sensitivity analysis was not performed due to insufficient data*" or "*We intended to perform sensitivity analyses for missing data and study quality where appropriate data existed*" but they failed to define study quality.

Table 2. Prevalence of different standard and nonstandard risk of bias domains that were specified as key domains for judging overall risk of bias in Cochrane reviews

Domains	*N* (%)
Standard domains	
Random sequence generation	64 (60)
Allocation concealment	99 (93)
Blinding of participants and personnel	31 (29)
Blinding of outcome assessors	63 (59)
Incomplete outcome data	73 (68)
Selective reporting	20 (19)
Other bias	2 (2)
Nonstandard domains	
Presence of intention-to-treat analysis	6 (6)
Similarity of baseline measurements	5 (5)
Protection against contamination	2 (2)
No serious flaws (e.g., high attrition rate)	2 (2)
Use of subjective patient-reported outcomes	1 (1)
Similarity or avoidance of cointerventions	1 (1)
Acceptability of compliance	1 (1)
Independence of intervention from other changes	1 (1)
Possibility of intervention affecting data collection	1 (1)

Among 958 reviews that had reported they planned sensitivity analysis based on RoB, 427 (44.5%) defined individual RoB domains that would be used in such analysis, whereas the others did not define them: 264 (27.5%) based their sensitivity analysis on excluding high-risk studies, 125 (13%) reviews restricted the analysis to low RoB studies only by excluding unclear and high-risk studies from the analysis, and 142 (15%) reviews generally stated that the sensitivity analysis was conducted to analyze the impact of the level of bias on the results.

Among 427 Cochrane reviews that had reported they planned sensitivity analysis based on individual RoB domains, 127 (13%) reviews reported that this analysis was planned based on a single RoB domain, most commonly for allocation concealment (Table 3). In the remaining 300 (31%) reviews, Cochrane authors used combinations of several individual RoB domains for sensitivity analysis (Table 3).

3.3. Conducted sensitivity analyses based on risk of bias

Among the 951 Cochrane reviews that reported they had planned to conduct at least one sensitivity analysis to explore the effect of RoB or trial quality, for only 268 (28%) Cochrane reviews the results for sensitivity analyses related to RoB were actually reported. For the 683 (72%) Cochrane reviews, these results were not reported because the authors wrote in Methods that they did not have enough data for such analysis or they planned sensitivity analyses

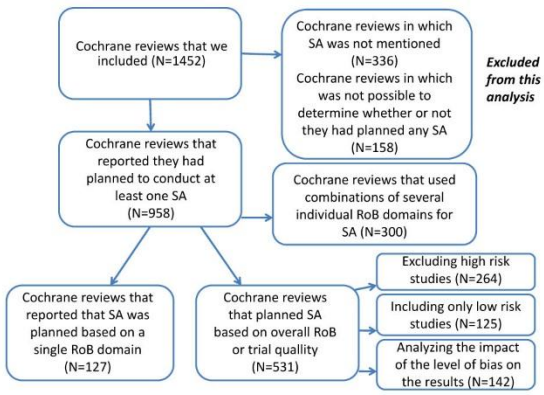

Fig. 1. Flow diagram: Number of Cochrane reviews that reported they had planned to conduct at least one sensitivity analysis to explore the effect of RoB or trial quality. RoB, risk of bias; SA, sensitivity analysis to explore the effect of RoB or trial quality.

Table 3. Risk of bias tool domains used in Cochrane reviews that had reported they planned sensitivity analysis based on RoB domains

Domains	N
Individual domains	
Allocation concealment	53
Incomplete outcome data[a]	49
Blinding[b]	15
Random sequence generation	8
Selective reporting	2
Several individual domains	
Allocation concealment and incomplete outcome data	63
Randomization and allocation concealment	48
Allocation concealment and blinding[c]	43
Allocation concealment, blinding[c], and incomplete outcome data	43
Randomization, allocation concealment, blinding,[c] and incomplete outcome data	30
Randomization, allocation concealment, and blinding[c]	27
Randomization, allocation concealment, and incomplete outcome data	26
Incomplete outcome data and selective reporting	5
Blinding[c] and incomplete outcome data	4
Randomization and incomplete outcome data	4
Randomization, allocation concealment, blinding[c], incomplete outcome data, and selective reporting	2
Randomization, allocation concealment, incomplete outcome data, and selective reporting	2
Allocation concealment, blinding[c], incomplete outcome data, and selective reporting	2
Randomization, blinding,[c] and incomplete outcome data	1

Abbreviation: RoB, risk of bias.

[a] Among the 49 reviews that used domain "incomplete outcome data" as the only RoB domain for sensitivity analysis, the authors defined percent of total number of participant dropouts as a threshold for low risk of attrition bias in a following way: 10% in three reviews, 12% in one review, 20% in fifteen reviews, 30% in one review, and 50% in two reviews; the remaining 27 reviews from this group did not provide a threshold regarding percent of participant attrition.

[b] Two reviews referred to blinding of participants and investigators, two reviews referred to blinding of outcome assessors, while eleven reviews not specifically stating what blinding were they referring to.

[c] In 152 of those reviews, "blinding" was used in RoB considerations for sensitivity analysis; in 79 reviews, it was blinding of outcome assessors, in 47, it was not specified to whom is this blinding concerned, in 15 reviews, it referred to blinding of participants and personnel, whereas in 11 reviews, it referred to blinding of participants, personnel, and outcome assessors.

related to RoB, but they failed to report why they did not actually do it.

However, it was often unclear whether these RoB-related sensitivity analyses referred to overall bias or individual domains. Among those 268 Cochrane reviews, in 181 (67.5%), the authors reported there were no differences between the primary analysis based on the RoB, in 56 (21%) reviews, the authors reported a significant change for at least one outcome after sensitivity analysis based on RoB; in 31 (11.5%) reviews, Cochrane authors reported minor differences from the first analyses that were not statistically significant.

3.4. Overall bias in a Cochrane RoB table

We found only two Cochrane reviews, which had included overall RoB assessment on study level in the Cochrane RoB table. One [8] had nine individual RoB domains in the table, and a tenth domain called "Total." In the domain "Total," Cochrane authors provided a judgment for overall RoB of each included RCT, and explanation for judgment included a note about the number of domains that were judged as having high, unclear, or low RoB. Another one [9] had ten domains, seven standard and "For-profit funding," "Overall risk of bias (mortality)," and "Overall risk of bias (nonmortality outcomes)."

4. Discussion

In this study, we analyzed methodological approaches of Cochrane authors regarding an assessment of overall bias on a study level in Cochrane reviews. The main finding of our study is that the minority of Cochrane authors mention an overall RoB assessment, even fewer actually make such overall judgment, and when they do, their assessment in most of the analyzed cases was not in line with the Cochrane Handbook.

According to the Cochrane Handbook [4], authors of Cochrane reviews should avoid summarizing the overall RoB. In spite of this recommendation, we found that a quarter of analyzed Cochrane reviews mentioned

assessment of overall RoB on the study level. Our findings are in line with previous research, which reported that Cochrane review authors sometimes assess overall RoB and conduct sensitivity analysis based on such assessment [5].

Although a quarter of Cochrane reviews mentioned assessment of overall RoB, most commonly, in more than a third of them, authors simply indicated that the RoB on the study level was assessed based on the criteria from the Cochrane Handbook, without specifying those criteria. Furthermore, none of those reviews reported that they had actually performed overall RoB assessment on a study level, and the only mention of such assessment remained in the Methods.

Bearing in mind that the Cochrane Handbook advises against summarizing overall bias, and authors are referring to the definition from the Handbook that they do not have, and ultimately did not report making such assessment, the question arises as to why almost 10% of analyzed Cochrane reviews contain such text.

Only a quarter of the reviews that mentioned overall bias assessment did it in line with Cochrane Handbook, that is, that the overall RoB assessment will depend on key domains, and they specified what they considered to be a key domain.

Some of them have mentioned key domains, without defining them, which casts doubt that some authors simply copy and paste the text about overall RoB from other reviews with no real intention to do assessment and Cochrane Groups do not take enough care to prevent this from happening.

On the other hand, there is one example such as Heal et al. [10] who are obviously aware of possible problems with assessing overall bias and clearly wrote "We acknowledge that there is no accepted definition of what constitutes a trial at high risk of bias" and after that have defined which key domains determine overall RoB in the studies included in their review.

It has been shown in multiple studies that methodology of Cochrane reviews is superior compared with non-Cochrane systematic reviews [11,12]. The Cochrane RoB tool is widely accepted, and it has been reported that it was used in 100% of Cochrane reviews and in 31% of non-Cochrane reviews published toward the end of 2014, but very often the tool was used in a nonrecommended way [5]. Multiple studies have shown that Cochrane reviews suffer from a high prevalence of inconsistencies related to RoB assessment [13–18]. This study further confirms those previous findings.

We found a highly inconsistent approach to the assessment of overall RoB on a study level in Cochrane reviews, many of which appear to contradict the advice given in the Cochrane Handbook. It has been already reported that published literature suffers from a simplified approach to overall RoB assessments such as treating all domains equally or implying that single domain with high RoB indicates that the whole study has high RoB [19].

Cochrane has developed Revised Cochrane risk of bias tool for randomized trials (RoB 2.0) [20]. RoB 2 is currently in the pilot phase, in which volunteer author teams use RoB 2 in RevMan Web. New tool contains a formal overall RoB judgment. The structure of the domains is somewhat different in the RoB 2.0 tool, with signaling questions that will have five answers. Based on those answers, software algorithm will assign RoB judgments to each domain, but this "software judgment" may be overridden. Because the new tool was not implemented yet in Cochrane reviews at the time when this article was completed, it remains to be seen how the new tool will be used, how will authors be trained for transition to the new tool, and what will Cochrane authors eventually do with it. Even after the new tool is formally adopted, it will take some time to see its results published. Because the updated RoB tool is much more complex, compared with the current version of the tool, it is questionable whether it will be widely adopted by the non-Cochrane systematic reviews.

In this study, we also found that the majority of analyzed Cochrane reviews planned sensitivity analysis to explore the effect of RoB/quality of included trials on results. This is in line with previous results [5]. However, only one-fifth of those reviews actually reported that they made such analysis, which is in line with the results of Jørgensen et al. [5]. Furthermore, many Cochrane reviews in our sample reported that they could not perform sensitivity analysis because there were few high-quality trials with "low" RoB.

Often, it was unclear whether the authors actually planned sensitivity analysis for RoB because they only mentioned "study quality," but then a reader cannot be sure whether they referred to RoB or any other measure of study quality. We would also like to highlight that approaches to making sensitivity analysis related to RoB were highly diverse. One particular cause for concern includes highly heterogeneous approaches in defining numerical indicators of participant attrition rate that are associated with a certain RoB judgment. Vague instructions from the Cochrane Handbook regarding an assessment of attrition bias might contribute to this observed heterogeneity [4,15].

These findings have very relevant practical considerations because Cochrane authors can yield different conclusions if they use different methods for summarizing overall RoB or if they make sensitivity analyses based on heterogeneous criteria. This can ultimately lead to questionable and inconsistent conclusions of Cochrane reviews, which are supposed to inform future practice and research.

In this study, we did not include non-Cochrane systematic reviews because those reviews, unlike Cochrane reviews, are not obliged to use the Cochrane methodology. Cochrane reviews are produced by a single organization, albeit one with a multitude of editorial review groups, which may lead to observed inconsistencies. However, Cochrane should implement strategies and interventions that will ensure that its reviews are produced within the clearly

defined expected standards and in compliance with recommendations from its Handbook.

Our study has several limitations. First, we used a convenience sample of a limited number of Cochrane reviews published within 3 years because we were interested in the snapshot of recently published reviews. Furthermore, we analyzed only Cochrane reviews and not their protocols. Some information that we were looking for in the reviews could have been reported in a protocol, that is, whether authors have planned to conduct overall RoB assessment or what kind of sensitivity analysis they had planned. However, even if Cochrane authors have subsequently decided to change some aspects of their methodology, or if they were unable to apply certain methodological approaches that they had planned, all of this should have been reported in a review.

In conclusion, a minority of Cochrane authors mentioned overall bias assessment, but only a quarter of them did it in line with recommendations from the Cochrane Handbook. Highly heterogeneous approaches to summarizing overall RoB on a study level and using RoB for sensitivity analyses may yield inconsistent and incomparable results across Cochrane reviews. Interventions for ensuring consistent use of systematic review methodology in Cochrane reviews process would be welcome and very relevant for practice and research, which rely on their conclusions for the advancement of medicine and future research.

CRediT authorship contribution statement

Andrija Babic: Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing - original draft, Writing - review & editing. **Ivana Vuka:** Data curation, Formal analysis, Writing - review & editing. **Frano Saric:** Data curation, Formal analysis, Writing - review & editing. **Ivona Proloscic:** Data curation, Formal analysis, Writing - review & editing. **Ema Slapnicar:** Data curation, Formal analysis, Writing - review & editing. **Jakica Cavar:** Data curation, Formal analysis, Writing - review & editing. **Tina Poklepovic Pericic:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing - original draft, Writing - review & editing. **Dawid Pieper:** Investigation, Methodology, Visualization, Writing - review & editing. **Livia Puljak:** Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Visualization, Writing - original draft, Writing - review & editing.

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Appendix ASupplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinepi.2019.11.008.

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