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Effects of integrated models of care for diabetes and hypertension in low- and middle-income countries. A systematic review

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Abstract

Objectives

To assess the effects of integrated models of care for people with multi-morbidity including at least diabetes or hypertension in low-and middle-income countries (LMICs) on health and process outcomes.

Design

Systematic review

Methods

We included randomised controlled trials (RCTs), non-RCTs, controlled before-after studies and interrupted time series (ITS) studies of people with diabetes and/or hypertension plus any other disease, in LMICs; assessing the effects of fully integrated care compared to partially or non-integrated care. We conducted a comprehensive search up to 12 December 2019. Two authors independently screened retrieved records; extracted data and assessed risk of bias. We conducted meta-analysis where possible or synthesised data narratively. We assessed the certainty of evidence using GRADE.

Results

We included five studies - two ITS studies and three cluster RCTs. Four studies conducted in Sub-Saharan Africa and one in India. Risk of bias was moderate. Integrated models of care compared to usual care (comparison 1) may make little or no difference to mortality, the number of people achieving blood pressure (BP) or diabetes control, and access to care; may increase the number of people who achieve both HIV and BP/diabetes control; and may have a very small effect on achieving HIV control. Interventions to promote integrated care compared to usual care (comparison 2) may make little or no difference to mortality, depression and quality of life, but the evidence is very uncertain. Interventions to promote integrated care compared to usual care may have little or no effect on HbA1c, systolic BP, and total cholesterol levels. Process outcomes were poorly reported.

Conclusions

Current evidence on the effects of integrated care on health outcomes is very uncertain. Programmes and policies on integrated care must consider context-specific factors related to health systems and populations.

PROSPERO registration: CRD42018099314

Strengths and limitations of this study

- We included study designs that are able to provide reliable evidence on the effects of integrated models of care on health and process outcomes
- We performed a comprehensive search for published and unpublished studies up to 12 December 2019, with no language restrictions.
- We assessed the certainty of evidence using the GRADE approach taking into consideration study limitations, inconsistency, imprecision, publication bias and indirectness when downgrading the certainty of evidence.

- Our review did not aim to answer questions on aspects linked to implementation of integrated models of care and barriers and facilitators to integrated models of care at individual and health-system level

Introduction

Low- and middle-income countries (LMICs) are facing an increasing burden of non-communicable diseases (NCDs).[1] A recent report of the World Health Organization (WHO) on NCDs indicates that 41 million people succumb to NCDs globally which is the equivalent of 71% of total global deaths. Fifteen million people die prematurely due NCDs every year (between the ages of 30 and 69 years) and 85% of these premature deaths occur in LMICs.[1 2] Furthermore, NCDs are projected to exceed communicable, maternal, perinatal, and nutritional diseases as the most common causes of death by 2030.[3] In LMICs, the vast majority of NCD deaths are caused by cardiovascular diseases (CVDs), mainly due to coronary artery diseases and stroke,[4] diabetes, cancer and chronic respiratory diseases; and they account for 54% of NCD disability adjusted life years.[1 5] Diabetes and hypertension are the major cardiovascular risk factors for target organ damage of brain, heart and kidney.[1]

Currently, it is estimated that 425 million people in LMICs live with diabetes. This number is expected to increase up to 629 million in 2045.[6] According to the International Society of hypertension (ISH), around 40% of people over age of 25 years have hypertension worldwide and two thirds of them live in LMICs.[7] Due to the existing high burden of communicable diseases, especially HIV infection, in sub-Saharan Africa, a lot of people are living with multi-morbidity. Because of the progress made with scaling up of anti-retroviral therapy (ART), the life expectancy of people living with HIV (PLHIV) has increased substantially, putting them at risk of NCDs that are common in older people. In addition to the traditional risk factors for NCDs, such as smoking, poor diet and a sedentary lifestyle, PLHIV have an increased risk of NCDs (especially CVD, cervical cancer, depression and diabetes), related to HIV itself and to ART related side effects[8-11] According to a recent systematic review examining the prevalence of NCDs among PLHIV in LMICs,[12] the pooled prevalence estimate of hypertension was 21.2% (95%CI 16.3 to 27.1); while that of depression was 24.4% (95%CI 12.5 to 42.1%). The prevalence of diabetes among PLHIV was reported to be between 1.2 and 18% and authors ascribed the variation in the findings to actual differences in populations, as well as the lack of standardised diagnostic criteria for diabetes.

In LMICs, people with NCDs such as diabetes and hypertension are generally characterised by very poor outcomes due to various other factors such as limited access to reliable healthcare services.[13] The chronic nature of NCDs puts strain on the already scarce resources of healthcare systems and affected individuals in LMICs.[14] Hence there is a need to design effective interventions to address the increasing burden of NCDs such diabetes and hypertension, in particular in complex patients with co-morbidities such as HIV infection and other CVDs. Provision of integrated care has been advocated by researchers and many international bodies such as the WHO as a way of tackling the rising burden of NCDs and strengthening the health systems particularly in LMICs.[15-17] Recent studies from LMICs have assessed integration of HIV/AIDS and tuberculosis (TB) services at primary healthcare (PHC) level.[18-20] Based on these integrated models of care, we conceptualised integrated care either as partial integration or full integration as illustrated in Figure 1.[21] Fully integrated care is seen as a "one-stop-shop" model whereby a patient receives all necessary care or services under one roof by one or more health-care professionals. In a partially integrated model of care, patients receiving treatment for one disease such as diabetes receive additional care related to either prevention, diagnosis or treatment of another disease, but do not receive the full package of care [21].

There are only a few systematic reviews to assess the effectiveness of integrated models of care in people with diabetes or hypertension and any other comorbid disease. We previously conducted a

scoping review to assess the evidence base[22] and did not identify any systematic review that included studies conducted in LMICs. Furthermore, none of the included studies assessed integrated care for diabetes or hypertension and communicable diseases (e.g. HIV). A subsequent systematic review by Haldane and colleagues examined existing programmes of integrated healthcare delivery for diabetes, hypertension or CVDs with HIV/AIDS.[23] However, included studies mostly described existing programmes with no thorough evaluation of the effectiveness of these programmes. A descriptive study from Cambodia looked at the management of HIV/AIDS, diabetes, and hypertension and found that integration of services for these conditions was highly acceptable and led to good health outcomes with improved CD4 count, glycated haemoglobin (HbA1c) and blood pressure levels.[24] Dudley and Garner[25] assessed the effectiveness of strategies to integrate PHC services in LMICs. They included studies that integrated family planning into existing services; nutrition and infectious disease interventions; and sexually transmitted infections (STIs), HIV/AIDS and TB treatment. None of the included studies reported on NCDs.

In light of limited information in existing reviews, we conducted this review to assess the effects of integrated models of care at PHC level for people living in LMICs, with multi-morbidity, of which diabetes or hypertension is one, compared to no integrated care on health and process outcomes.

Methods

Our systematic review followed the methods pre-specified in a published protocol.[21] We followed the PRISMA reporting guideline to report on the findings of our systematic review.

We included studies with adults and children attending PHC clinics, presenting with diabetes or hypertension plus one or more other chronic diseases (multi-morbidity), or risk factors for other chronic diseases in LMICs. We defined LMICs according to the World Bank.[26] Eligible interventions were models of full or partial integration of services at PHC and community level. Partial integration of services was defined as models where patients treated for diabetes, hypertension, or any other chronic disease received part of the package of care (prevention, diagnosis, treatment) for another disease. Full integration of service delivery was defined as models where patients (primarily treated for diabetes, hypertension or any other disease) received the full package of care (prevention, diagnosis and treatment) for diabetes or hypertension and any other chronic disease at the same point of care by one or more healthcare professionals. In addition, we considered interventions that promoted an integrated approach to providing care for multiple conditions. We considered studies that compared fully integrated models of care to stand-alone care; partially integrated models of care to stand-alone care; fully integrated models of care to partially integrated models of care; and interventions that promoted integrated care compared to usual care. Randomised controlled trials (RCTs), including cluster RCTs, controlled (non-randomised) clinical trials (CCTs) or cluster non-randomised trials, interrupted time series (ITS) studies with at least three data points before and after the intervention, and controlled before-and-after (CBA) studies were eligible for inclusion. Cluster randomised, cluster non-randomised or CBA studies were only included if there were at least two intervention sites and two control sites. We included studies that reported on either primary or secondary outcomes, as defined and reported by primary study authors. Primary outcomes were all-cause mortality, disease specific morbidity as reported in included studies (e.g. disease control metrics), quality of life, glycated haemoglobin (HbA1c), systolic Blood pressure (SBP) and cholesterol levels. Secondary outcomes were access to care, retention in care, adherence, continuity of care, quality of care and cost of care.

We searched MEDLINE (PubMed), EMBASE (Ovid), the Cochrane Central Register of Controlled Trials (CENTRAL), LILACS, Africa-Wide Information (via EBSCO host), CINAHL, and Web of Science (Core collection) (Date of last search: 12 December 2019). We searched the WHO International Clinical Trials Registry Platform (ICTRP) and Clinicaltrials.gov for ongoing studies, as well as conference

abstracts from the International AIDS Society Online Resource Library, the HIV/AIDS Implementers' Meetings and the NCDs Alliance meetings. Search terms included 'diabetes', 'hypertension', 'comorbidities , 'integrated health care delivery', 'low-and middle-income countries' and their synonyms. The full search strategy for MEDLINE (Pubmed) is provided in Supplementary file 1. To supplement the search of electronic databases, we screened reference lists of included studies and reference lists of relevant systematic reviews, and contacted experts in the field and relevant organisations (e.g. NCD Alliance) for unpublished studies. We did not have any restrictions related to language or publication status.

Two authors (JUN and AR or a research assistant) independently screened titles and abstracts of studies identified by the search, using Covidence software.[27] We retrieved full texts of potentially eligible studies. Two authors (JUN and AR/TY/CMB) independently screened full texts for eligibility. Discrepancies were resolved through discussion with a third author (JJM/IT). We classified studies as included, excluded or ongoing and provided reasons for excluding studies.

Two authors (JUN, AR and IT) independently extracted data for included studies using a pre-specified, piloted data extraction form and assessed risk of bias. Discrepancies were resolved through discussion or by consulting a third author (TY/JJM). We extracted data related to the study design, participants, intervention, comparison, outcomes, setting, context and funding sources. We used the template for intervention description and replication (TIDieR)[28] and the PRISMA-Complex Interventions extension checklist[29] to guide data extraction and reporting related to the interventions. We used guidance from Cochrane Effective Practice and Organisation of Care (EPOC) to assess risk of bias for included studies[30]. Risk of bias was assessed as low, high, or unclear for each domain. For RCTs, non-randomised trials and CBA studies, we assessed the following nine domains: 1) random sequence generation, 2) allocation concealment, 3) baseline outcome measurements, 4) baseline characteristics, 5) incomplete outcome data, 6) knowledge of allocated intervention (blinding), 7) protection against contamination, 8) selective outcome reporting and 9) other risks of bias. For cluster RCTs, we assessed additional risk of bias linked to recruitment, cluster baseline differences, loss of clusters, incorrect analysis and compatibility with RCTs randomised by individuals, as per the Cochrane handbook.[31] For ITS studies, we assessed whether 1) the intervention was independent of other changes, 2) the shape of the intervention effect was pre-specified, 3) the intervention was unlikely to affect data collections, 4) knowledge of the allocated intervention was adequately prevented during the study, 5) incomplete outcome data was likely to bias results, 6) outcomes were reported selectively and 7) there were any other risks of bias.

We extracted relevant data for each outcome per included study. For dichotomous outcomes, we reported risk ratios (RR) and 95% confidence intervals (CI). For continuous outcomes, we reported mean differences (MD) with 95% CI if outcomes were measured in the same way across studies, or standardised mean differences (SMD) with 95% CI where outcomes were measured differently across studies and where standard deviations (SD) were reported. For ITS studies, we reported beta coefficients (β) with standard error (SE). We contacted study authors to request information on missing data. We did not impute any data.

All included cluster RCTs appropriately adjusted for the effects of clustering in their analysis, we thus used these adjusted effect estimates and standard errors in our meta-analysis using the generic inverse-variance method in Review Manager 5.[32] We did not include studies with more than one treatment arm in our review.

We explored clinical heterogeneity by clearly documenting study characteristics related to the population, intervention, outcomes and context in table format. We assessed statistical heterogeneity in each meta-analysis by inspecting forest plots and calculating Chi^2 test values and I^2 statistics. We considered heterogeneity to be significant if the p-value of the Chi^2 test was < 0.10, and the I^2 statistic was above 30%, as per the recommendations in the Cochrane handbook.[31]

We pooled data from individual studies if we judged them to be sufficiently homogeneous in terms of design, population, intervention and comparator. As we anticipated some degree of heterogeneity, we performed random-effects meta-analysis. We did not pool data from RCTs and non-randomised studies in a single meta-analysis. Where we judged included studies to be too heterogeneous to pool, we used narrative synthesis and presented data in tabular format. We did not perform subgroup or sensitivity analysis, as only two studies contributed to the meta-analysis. We were unable to examine reporting biases by means of funnel plots, as we only included two studies in the meta-analysis.

We assessed the certainty of the evidence using GRADE[33] for the following outcomes: mortality, disease specific morbidity, quality of life, HbA1c, systolic BP, cholesterol levels and access to care. We created a 'Summary of findings' table using GRADEpro software.[34] Our judgements to downgrade the certainty of evidence were based on assessment of the following five domains: 1) study limitations, 2) inconsistency, 3) imprecision, 4) indirectness and 5) publication bias. We considered upgrading the certainty of evidence for non-randomised studies if there was a large effect, a dose-response and cases where all plausible residual confounding would reduce a demonstrated effect or would suggest a spurious effect if no effect was observed. For each outcome, we described the certainty of evidence as high, moderate, low or very low .[35]

Patient and public involvement

No patients were involved in this systematic review.

Results

The results of the search are depicted in the PRISMA flow diagram (Figure 2). We screened titles and abstracts of 7568 records. We obtained and screened full texts of 49 potentially relevant studies. We included five studies,[36-40] (Table 1) reported in six articles and excluded 37 articles with reasons (Table 2). For one study[41] that met eligibility criteria, we were only able to access the conference abstract. We classified this study as 'awaiting assessment', as we are unable to definitively decide on inclusion or exclusion until we have access to the full report. We identified five ongoing RCTs,[42-45] investigating integrated care for depression and hypertension in China;[42] integrated care for depression and hypertension[43] or depression and diabetes/HIV[44] in South Africa; integrated care for common mental disorders and hypertension, diabetes or ischemic heart disease in India;[45] and diabetes and TB in India.[46]

Table 1: Summary of characteristics of included studies

Study ID	Study design	Country and Setting	Participants	Intervention	Control	Study duration (follow-up)	Outcomes[1]
Integrated models of care							
Ameh 2017[36]	Controlled ITS study	South Africa: Primary health care (PHC) facilities, Ehlanzeni health district, Mpumalanga Province	Patients with chronic disease (HIV, diabetes or hypertension) n=878	Integrated chronic disease management (ICDM) model Clinics: n=7 Participants: n=435	Usual care in PHC facilities Clinics: n=5 Participants: n=443	30 months Pre-intervention: 6 months Post-intervention: 24 months	- **Blood pressure (BP) control[2]** - **CD4 count control[3]** - **Number of healthcare visits**
Havlir 2019[40]	Cluster RCT	Kenya and Uganda: Rural regions in south-western and eastern Uganda, and western Kenya	Clusters: Communities of 9000 to 11 000 people Participants: People residing in community n=150 395 (baseline)	Integrated care: Baseline HIV and multi-disease testing plus annual testing, universal ART and streamlined, patient-centered care Clusters: n=16 Participants: n=79 818 (baseline)	Usual care: Baseline HIV and multi-disease testing and national guideline-restricted ART, hypertension and diabetes care as per country standard of care (not integrated) Clusters: n=16 Participants: n=70 577 (baseline)	36 months	- Cumulative HIV incidence - Time to initiation of ART - Viral suppression - **Death** - Incident tuberculosis or death due to illness - **Control of hypertension[4] among HIV-infected persons** - **Control of diabetes[5] or hypertension (NCD) among HIV infected persons** - **Control of HIV[6] and hypertension** - **Control of HIV and NCDs[7]** - Control of hypertension in the overall population - Control of diabetes in the overall population

[1] Outcomes relevant to this review are in bold
[2] Defined as: BP <140/90mmHg
[3] Defined as: CD4 count >350 cells/mm^3
[4] Defined as: At least one systolic BP measurement <140mmHg, and at least one diastolic measurement of <90mmHg
[5] Defined as: Finger prick blood glucose ≤11 mmol/L
[6] Defined as: Suppressed viral replication (<500 copies/ml)
[7] Defined as: Control of all prevalent NCDs (hypertension or diabetes)

Rawat 2018[39]	ITS study	South Africa: PHC clinics in the Free state Province	Patients attending PHC clinics (focus on diabetes and hypertension) n=not reported	Integration of HIV care into HC facilities n=131 clinics	No control group	48 months Pre-intervention: 12 months Post-intervention: 36 months	- **Population level new diabetics on treatment** - **Clinic level new diabetics on treatment** - **Population-level new hypertensive on treatment** - **Clinic level new hypertensive on treatment** - **Total ART patients** - **New patients initiated on ART**
Interventions to promote integrated delivery of care							
Fairall 2016[37]	Cluster RCT	South Africa: Mostly rural PHC clinics in Eden and Overberg districts, Western Cape Province	Patients with one or more of the following: hypertension, diabetes, chronic respiratory disease, depression n=4393	Primary Care (PC) 101 management tool Clinics: n=19 Participants: n=2166	Usual care: Practical Approach to Lung Health and HIV/AIDS in South Africa (PALSA PLUS) management tool Clinics: n=19 Participants: n=2227	14 months	- Treatment intensification for hypertension, diabetes and chronic respiratory disease - **Depression** - CVD risk - **Systolic BP** - **HbA1C** - Body Mass Index (BMI) - Smoking status - **Health-related quality of life** - **Mortality** - **Healthcare utilisation**
Prabhakaran 2019[38]	Cluster RCT	India: Community Health Centres (CHC) from 4 districts in Haryana and 2 districts in Karnataka	Patients with confirmed diagnosis or hypertension n=3698	mWellcare system CHCs: n=20 Participants: n=1842	Enhanced usual care CHCs: n=20 Participants: n=1856	12 months	- **Mean change in systolic BP** - **Mean change in HbA1C** - Mean change in fasting plasma glucose - **Mean change in total cholesterol** - Mean change in CVD risk - Mean change in Tobacco use - Mean change in BMI - Alcohol use - **Depression score** - **Adherence** - **Perceived quality of care**

Table 2: List of excluded studies

Studies excluded for wrong population	Studies excluded for wrong study design	Studies excluded for wrong intervention
Abrahams-Gessel 2018[47]	Ajay 2016[54]	Bachmann 2018[73]
Adomaviciute 2014[48]	Al Asmary 2013[55]	Hong 2013[74]
Alharbi 2014[49]	Garrib 2018[56]	Kowalski 2017[75]
Miao 2016[50]	Germe 2017[57]	McKee 2011[76]
Myers 2018[44]	Kwarisiima 2019[58]	Mendis 2010[77]
Rakic 2011[51]	Li 2013[59]	Pibernik-Okanovic 2015[78]
Sarrafzadegan 2006[52]	Mahomed 2014[60]	Saleh 2018[79]
Spaak 2017[53]	Narayanan 2012[61]	Sarrafzadegan 2009[80]
	Nigatu 2012[62]	Tourkmani 2018[81]
	Nyabera 2011[63]	Wenxi 2017[82]
	Patel 2018[64]	
	Patel 2015[65]	
	Rabkin 2018[66]	
	Samb 2010[67]	
	Sarraf-Zadegan 2003[68]	
	Sushilkumar 2015[69]	
	Tedjokusumo 2003[70]	
	Tiam 2012[71]	
	Wasay 2009[72]	

Characteristics of included studies

We included three cluster RCTs and two ITS studies. One cluster RCT was conducted in South Africa,[37] one in India,[38] and the Sustainable East Africa Research in Community Health (SEARCH) trial was conducted in Uganda and Kenya.[40] The two ITS studies were both conducted in South Africa[36 39] (Table 1). All studies were conducted in PHC facilities in mostly rural settings. All five studies assessed the effect of strategies for full integration of care compared to partial integration of care.

The two ITS studies[36 39] and the SEARCH trial[40] assessed the effects of integrated models of care for chronic diseases (Table 3). Ameh and colleagues[36] conducted a controlled ITS study, comparing the integrated chronic disease management (ICDM) model to usual care over a period of 30 months. Rawat and colleagues[39] examined the effect of integrating HIV care into PHC clinics over a 48 months period. The SEARCH trial[40] assessed the effects of universal ART and streamlined, patient-centered care (integrated care) compared to usual care as per national guidelines. Interventions are described in more detail according to the TiDIER checklist in supplementary file 2.

The other two cluster RCTs[37 38] assessed the effectiveness of interventions to promote integration of care (Table 3). Fairall and colleagues[37] introduced the Primary Care (PC) 101 clinical management tool to promote provision of comprehensive care for all symptoms including NCDs, HIV, TB, mental health and women's health, in PHC clinics randomised to the intervention, while the control clinics continued using the Practical Approach to Lung Health and HIV/AIDS in South Africa (PALSA PLUS) management tool, which did not cover all NCDs and was the standard of care at the time of the trial. Prabhakaran and colleagues[38] introduced the mWellcare system, a m-health based electronic decision support system, to promote integrated management of hypertension, diabetes, depression,

and alcohol and tobacco use in PHC centres randomised to the intervention. Control centres continued with usual care. Interventions are described in more detail in supplementary file 3.

Table 3: Key components of included interventions

Name and Study ID	**Components related to provision of care in the clinic**	**Components related to provision of care in the community/at home**	**Training**	**Appointment reminders**
Integrated chronic disease management (ICDM) model Ameh 2017	Facility reorganisation: designated chronic care area; supply of critical medicines; pre-packaging of medication Clinical management support: use of guidelines to manage chronic diseases (PC101); human resources audit; capacity building; appropriate referral	Ward-based outreach teams to ensure individual responsibility and "assisted" self-management Health promotion and population screening	-	-
National policy to integrate HIV care into all PHC facilities Rawat 2018	Policy to integrate HIV care into PHC clinics Either disease-specific nurses in separate consulting rooms (co-location), or one nurse that provided comprehensive care for all diseases in single consultation room Additional staff to strengthen drug delivery systems	-	Training of nurses in comprehensive management of HIV: Nurse initiated Management of ART (NIMART) Training of nurses through the Practical Approach to Lung Health in South Africa (PALSA PLUS)	-
SEARCH intervention Havlir 2019	Patient-centered, integrated care for HIV, diabetes, hypertension: 3-month visit intervals; ART to all HIV positive participants; hypertension and diabetes treated according to standard algorithms	Community health campaigns (CHCs): Testing for HIV, diabetes and hypertension; counselling and clinic appointments; blood tests for HIV positive participants; transportation voucher for first clinic visit	-	Phone/SMS reminders about clinic visits

		Home-based testing for participants that did not attend CHCs Appointments to initiate ART within 7 days for HIV positive participants not on ART; introductory phone call from clinic staff; support hotline available via phone or text message		
Primary Care (PC) 101 Fairall 2016	PC 101 guideline: Ring-bound, colour illustrated booklet Expanded prescribing provisions for nurses Desk pads with key messages	-	Training of facility trainers Educational outreach sessions by facility trainers	Letters and SMS reminders of follow-up visits
mWellcare Prabhakaran 2018	mWellcare system: m-Health-based electronic decision-support system Visible charts on the management of the conditions Onsite supervision and support	Pamphlets containing lifestyle advice	Training of physicians on current clinical management guidelines and orientation to mWellcare Training of nurses in management of hypertension, diabetes, depression, and tobacco and alcohol use	SMS reminders of follow-up visits and medication adherence

Risk of bias in included studies

For the two ITS studies, we judged risk of bias to be low or unclear in all domains (Figure 3). For the three cluster RCTs, we judged risk of selection bias to be low, risk of performance bias to be high, as blinding of participants and personnel was not possible due to the nature of the interventions, and risk of detection bias to be unclear for all three studies. We judged attrition bias to be low for two cluster RCTs[37 38] and unclear for the SEARCH trial[40] (Figure 4). Detailed judgements for each included study are reported in supplementary file 4.

Integration of chronic disease services compared to usual care

We included three studies as part of this comparison.[36 39 40] Results are summarised in the summary of findings table (Table 4) and forest plots are available in supplementary file 5.

Table 4: Summary of findings for integrated models of care compared to usual care for diabetes and hypertension in LMICs

Patient or population: Patients with multi-morbidity (diabetes and/or hypertension and other chronic conditions e.g. HIV)
Setting: Low- and middle-income countries
Intervention: Integrated care for hypertension, diabetes and HIV
Comparison: Usual care

Outcome	Effect			No of participants (studies)	Certainty of evidence (GRADE)	Comments
	Risk with usual care	Risk with integrated care	Relative effect (95% CI)			
Mortality	0.56 per 100 person-years	0.51 per 100 person-years	RR 0.90 (0.79 to 1.02)	171 431 (1 RCT)	⨁◯◯◯ VERY LOW a,b,c	Integrated care compared to usual care may make little or no difference to the rate of death, but the evidence is very uncertain
BP control (number of people achieving BP control)	The RCT showed no effect, while the ITS study showed a very small effect			2319 (2 studies: 1 RCT, 1 ITS study)	⨁◯◯◯ VERY LOW a,c,d,e,f	Integrated care compared to usual care may make little or no difference to achieving BP control but the evidence is very uncertain
BP or diabetes (NCD) control (number of people achieving NCD control)	There was no effect among PLHIV with prevalent NCD at baseline and at follow-up			1 RCT*	⨁◯◯◯ VERY LOW a,c,d	Integrated care compared to usual care may make little or no difference to achieving NCD control but the evidence is very uncertain
HIV control (CD4 count control)	The probability of CD4 count control was 6% greater in intervention clinics compared to control clinics			878 (1 ITS study)	⨁◯◯◯ VERY LOW e,f	Integrated care may have a very small effect on achieving CD4 count control, but the evidence is very uncertain
BP and HIV control (number of people achieving both HIV viral suppression and BP control)	There was a small effect among PLHIV with prevalent hypertension at baseline and at follow-up			1441 (1 RCT)	⨁◯◯◯ VERY LOW a,c,d	Integrated care compared to usual care may result in a slight increase in the number of people achieving both BP and HIV control but the evidence is very uncertain
BP or diabetes (NCD) and HIV control (number of people achieving both HIV viral suppression and NCD control)	There was a small effect among PLHIV with prevalent hypertension at baseline and at follow-up			1441 (1 RCT)	⨁◯◯◯ VERY LOW a,c,d	Integrated care compared to usual care may result in a slight increase in the number of people achieving both NCD and HIV control but the evidence is very uncertain
Quality of life	-			-	-	Not reported
Systolic BP	-			-	-	Not reported
HbA1c	-			-	-	Not reported
Cholesterol levels	-			-	-	Not reported

Access to care	There was no change in trend from pre- to post-intervention for population level new diabetics on treatment, clinic level new diabetics on treatment and clinic-level new hypertensive patients on treatment. There was a slight decrease in new hypertensive patients on treatment at population level at 36 months	1 ITS*	⊕◯◯◯ VERY LOW [e,g]	Integrated care may make little or no difference to short term access to care and may result in a slight decrease in long-term access to hypertensive care, but the evidence is very uncertain.

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; BP: Blood pressure; HIV: Human Immunodeficiency Virus; HbA1c: Glycated Haemoglobin; NCD: Non-communicable disease; RCT: Randomised controlled Trial; ITS: Interrupted time series

*Sample size not reported

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Footnotes: Explanation of GRADE certainty of evidence

a) Downgraded by 1 due to high risk of performance bias and unclear risk of bias for other domains
b) Downgraded by 1 due to indirectness: Results are based on number of participants at baseline, however authors did not report how many participants had HIV plus hypertension/diabetes at baseline. At 3-year follow-up, less than 1% of participants at follow-up had hypertension/diabetes and HIV infection (0.7% (694/103 777) in the control group and 0.6% (747/121 347) in the intervention group)
c) Downgraded by 1 due to indirectness: Usual care comprised care according to national guidelines in Kenya and Uganda. Authors did not report what this entails. It is not clear to what extend care was integrated or not
d) Downgraded by 1 due to imprecision: Small sub-sample with hypertension and HIV in the RCT with wide 95% confidence intervals
e) Observational study, starting at low certainty evidence
f) Downgraded by 1 due to indirectness: Intervention clinics experienced stock-outs of anti-hypertensive drugs and malfunctioning of BP machines. We are therefore not confident that the intervention was delivered as intended
g) Downgraded by 1 due to indirectness: Study reported on population level new diabetics on treatment, clinic level new diabetics on treatment, population level new hypertensive patients on treatment and clinic level new hypertensive patients on treatment. This is an indirect measure of access to care

The SEARCH trial[40] reported the rate of all-cause mortality among baseline residents in included communities. Results suggest that integrated compared to usual care may make little or no difference to the mortality rate when compared to usual care but the evidence is very uncertain (RR 0.90 95%CI 0.79 to 1.02, n=171 431, 1 RCT, very low-certainty evidence).

Integrated care compared to usual care may make little or no difference to achieving BP control, but the evidence is very uncertain. Results from the SEARCH trial[40] suggest that integrated care compared to usual care may make little or no difference to the number of PLHIV who achieve BP control with prevalent hypertension at baseline (RR 1.09, 95%CI 0.98 to 1.21, 1 RCT, very low-certainty evidence) and PLHIV with prevalent hypertension at follow-up (RR 1.16, 95%CI 0.99 to 1.36, n=1441, 1 RCT, very low- certainty evidence). Results of the controlled ITS study[36] suggest that integrated care compared to usual care may increase the probability of achieving BP control by 1%, but the evidence is very uncertain (β=0.010, 95%CI 0.003 to 0.016, n=878, 1 ITS study, very low-certainty evidence).

Results from the SEARCH trial [40] suggest that integrated care compared to usual care may make little or no difference to the number of PHLV who achieve NCD (diabetes and/or hypertension) control with prevalent NCD at baseline (RR 1.06, 95%CI 0.88 to 1.27, 1 RCT, very low-certainty evidence) and prevalent NCD at follow-up but the evidence is very uncertain (RR 1.13, 95%CI 0.97 to 1.32, 1 RCT, very low-certainty evidence).

One ITS study[36] reported on HIV control in terms of CD4 count control. Results suggest that integrated care compared to usual care may increase the probability of achieving CD4 count control by 6%, but the evidence is very uncertain (β=0.057, 95%CI 0.056 to 0.058, n=878, 1 ITS study, very low-certainty evidence).

Results from the SEARCH trial[40] suggest that integrated care compared to usual care may increase the number of PLHIV who achieve both HIV viral suppression (HIV control) and BP control with prevalent hypertension at baseline (RR 1.22, 95%CI 1.08 to 1.37, 1 RCT, very low-certainty evidence) and with prevalent hypertension at follow-up (RR 1.24, 95%CI 1.10 to 1.40, n=1441, 1 RCT, very low-certainty evidence). Integrated care compared to usual care may make little or no difference to the number of PLHIV who achieve both HIV viral suppression (HIV control) and NCD control with prevalent NCD at baseline (RR 1.18, 95%CI 0.97 to 1.44, 1 RCT, very low certainty), but may result in a slight increase in the number of PLHIV who achieve both HIV viral suppression (HIV control) and NCD control with prevalent NCD at follow-up (RR 1.24, 95%CI 1.10 to 1.40, 1 RCT very low-certainty evidence). However, the evidence is very uncertain for these outcomes.

One ITS study reported on access to care[39] in terms of the change in post-integration trend compared to pre-integration trend for population level new diabetics on treatment, clinic level new diabetics on treatment, population-level new hypertensive patients on treatment, and clinic level new hypertensive patients on treatment. Integrated care may make little or no difference to population level new diabetics on treatment at 18 (1/100 000, Standard Error (SE)=2, p=0.50, very low certainty) and 36 months (1/100 000, SE=3, p=0.61, very low-certainty evidence) post-integration; clinic level new diabetics on treatment at 18 (0/100 000, SE=1; p=0.96, very low-certainty evidence) and 36 months post-integration; clinic level new hypertensive patients on treatment at 18 (0/100 000, SE=1; p=0.78, very low-certainty evidence) and 36 months (0/100 000, SE=0; p-value=0.57, very low-certainty evidence) post-integration, and population level new hypertensive patients on treatment at 18 months post-integration (-7/100 000, SE=4; p=0.08, very low-certainty evidence). Results suggest that there was a slight decrease in population level new hypertensive patients on treatment at 36 months post-integration (-6/100 000; SE=3; p=0.02, very low-certainty evidence). However, the evidence is very uncertain for these outcomes.

Authors also reported on the total number of patients on anti-retroviral treatment (ART) and the number of new patients initiated on ART. Overall, the number of patients for both outcomes increased during each year of follow-up. No effect size was reported. No other secondary outcomes were reported for this comparison.

Interventions promoting integrated care compared to usual care

We included two studies in this comparison.[37 38] Results are summarised in the summary of findings table (Table 5) and forest plots are available in supplementary file 4.

Results from one cluster RCT[37] suggest that interventions to promote integrated care compared to usual care may make little or no difference in mortality (RR 1.11; 95% CI 0.79 to 1.56; n=3393; 1 RCT, very low-certainty evidence) when compared to usual care, but the evidence is very uncertain.

Results from two RCTs[37 38] suggest that interventions to promote integrated care compared to usual care may make little or no difference to depression scores, but the evidence is very uncertain. Fairall

2016 reported the change in depression scores from baseline to follow up using the 10-item Center for Epidemiologic Studies Depression Scale and reported no difference between groups (MD −0.12; 95%CI −1.72 to 1.48; n=3976, very low-certainty evidence). Prabhakaran 2019 measured depression scores at follow-up using the Patient Health Questionnaire-9 and reported no difference between groups (MD -1.6; 95%CI -4.4 to 1.2; n=3324, very low-certainty evidence).

Results from one RCT[37] suggest that interventions to promote integrated care compared to usual care may make little or no difference to quality of life, but the evidence is very uncertain. The RCT reported on the change in health-related quality of life from baseline to follow-up using the EuroQol-5D visual analogue scale and the EuroQol-5D index score. There was no difference between groups, neither for the Euro-Qol-5D visual analogue scale (MD 6.06; 95%CI -3.25 to 15.36; n=3969, very low-certainty evidence) nor for the EuroQol-5D index score (MD 0.00; 95%CI -0.05 to 0.06; n=3969, very low-certainty evidence).

Table 5: Summary of findings for interventions to promote integrated care compared to usual care for diabetes and hypertension in LMICs

Patient or population: Patients with diabetes, hypertension and other chronic diseases
Setting: Low- and middle-income countries
Intervention: Strategies to promote integrated care
Comparison: Usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care	Risk with Strategies to promote integrated care				
Mortality	29 per 1,000	**32 per 1,000** (23 to 45)	**RR 1.11** (0.79 to 1.56)	4393 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	Integrated care compared to usual care may make little or no difference to the risk of death, but the evidence is very uncertain
Depression	One study reported change in depression scores using the 10-item Center for Epidemiologic Studies Depression Scale and the other study reported depression scores at follow-up using the Patient Health Questionnaire-9. Both studies showed no effect.			7293 (2 RCTs)	⊕◯◯◯ VERY LOW [a,b,c]	Integrated care compared to usual care may make little or no difference to depression scores, but the evidence is very uncertain
Change in quality of life (Euro-Qol-5D visual analogue scale)	Quality of life scores with usual care improved by a mean of 6.4 points	The mean change in quality of life with integrated care was **6.06 points higher** (3.25 points lower to 15.36 points higher)	-	3969 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	Integrated care compared to usual care may make little or no difference in quality of life, but the evidence is very uncertain
Change in HbA1c	The mean change in HbA1c with usual care ranged from -0.58 to -0.2%	The mean change in HbA1c with integrated care was **0.11 % higher** (0.2 lower to 0.42 higher)	-	1687 (2 RCTs)	⊕⊕◯◯ LOW [a,c]	Integrated care compared to usual care may have little or no effect on HbA1c
Change in systolic BP	The mean change in systolic BP with usual care ranged from -13.7 to -1.1 mmHg	The mean change in BP with integrated care was **1.11 mmHg higher** (1.14 lower to 3.35 higher)	-	4807 (2 RCTs)	⊕⊕◯◯ LOW [a,c]	Integrated care compared to usual care may have little or no effect on systolic BP

Change in total cholesterol	The mean change in total cholesterol with usual care was 2.0 mg/dl	The mean change in total cholesterol with integrated care was **2.5 mg/dl lower** (7.1 lower to 2.1 higher)	-	3324 (1 RCT)	⊕⊕◯◯ LOW [a,c]	Integrated care compared to usual care may have little or no effect on total cholesterol levels

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **BP**: Blood pressure; **HbA1c**: Glycated haemoglobin; **RCT**: Randomised controlled trial
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Footnotes: Explanation of GRADE certainty of evidence

a. Downgraded by 1 due to high risk of performance bias and unclear risk of bias in some other domains
b. Downgraded by 1 due to imprecision: study not adequately powered for this outcome, small sample size and wide 95% CI
c. Downgraded by 1 due to indirectness: The interventions comprised strategies to promote integrated care at clinic level, and not integrated models of healthcare delivery at health system level

Results from two cluster RCTs[37 38] suggest that interventions to promote integrated care compared to usual care may have little or no effect on change in HbA1c from baseline to follow-up (MD 0.11%; 95%CI -0.20 to 0.42; n=1687; 2 RCTs, low-certainty evidence).

Results from two cluster RCTs[37 38] suggest that interventions to promote integrated care compared to usual care may have little or no effect on change in systolic BP from baseline to follow-up (MD 1.11mmHg; 95%CI -1.41 to 3.35; n=4807; 2 RCTs, low-certainty evidence).

Results from one cluster RCT[38] suggest that interventions to promote integrated care compared to usual care may have little or no effect on change in total cholesterol from baseline to follow-up (MD -2.50mg/dl; 95%CI -7.10 to 2.10; n=3324; low-certainty evidence).

Fairall 2016 reported the number of clinic visits three months before the follow-up interview and found no difference between groups (incidence rate ratio 1.02; 95%CI 0.93 to 1.13; n=3121).

One cluster RCT reported absolute numbers for drug adherence during the past seven days.[38] Patients in the intervention group reported greater adherence for both hypertensive drugs (833/1027; 81.1% vs. 648/1119; 57.9%) and anti-hyperglycemic drugs (683/829; 82.4% vs. 570/827; 68.9%) compared to patients receiving usual care.

One cluster RCT[38] reported on perceived change in quality of care as a composite perception on availability of drugs, guidance from physicians, quality of care, frequency of blood pressure measurement, and care provided by NCD nurses. Perceived quality of care improved in both groups. Patients receiving integrated care (n=1637), reported that quality of care was slightly/much better (96.6%), about the same (3.3%) and somewhat/much worse (0.2%). Patients receiving usual care (n=1687) reported that quality of care was slightly/much better (95%), about the same (4.4%) and somewhat/much worse (0.5%).

Neither of the two cluster RCTs included in this comparison reported on access to care, continuity of care or cost of care.

Discussion

We included five studies and two comparisons in this review. Three studies were conducted in South Africa, one in India and one in Kenya and Uganda. Two ITS studies and one cluster RCT provided data for the first comparison, integration of chronic disease services compared to usual care. Results suggest that integrated models of care compared to usual care may make little or no difference to mortality, the number of people achieving blood pressure (BP) or diabetes control, and access to care; may increase the number of people who achieve both HIV and BP/diabetes control; and may have a very small effect on achieving HIV control. However, the evidence for all outcomes is very uncertain. Two cluster RCTs provided data for the second comparison, interventions promoting integrated care compared to usual care. Results suggest that interventions to promote integrated care compared to usual care may make little or no difference to mortality, depression and quality of life, but the evidence is very uncertain. Interventions to promote integrated care compared to usual care may have little or no effect on HbA1c, systolic BP, and total cholesterol levels. Process outcomes were poorly reported across included studies, with none of the studies reporting on continuity of care or cost of care.

We followed a rigorous and systematic process according to standard systematic review methods. We performed a comprehensive search of published and unpublished studies up to 12 December 2019, with no language restrictions. We assessed the certainty of evidence using the GRADE approach across outcomes, taking into consideration study limitations, inconsistency, imprecision, publication bias and indirectness when downgrading the certainty of evidence.

Other systematic reviews that assessed the effects of integrated models of care on health outcomes in LMICs had similar findings. Dudley and Garner[25] assessed strategies to integrate PHC services on healthcare delivery and health status in LMICs. They found no evidence that integrated services improved healthcare delivery or health status. However, none of the included studies assessed integrated care for NCDs. Haldane and colleagues[23] described existing integrated models of care for HIV and NCDs and assessed health outcomes, barriers and facilitators. However, most of the included studies were descriptive or observational and health outcomes were poorly reported. Indeed, they highlighted the need for rigorous research that includes long-term follow-up and the role of incentives.

Although we considered multi-morbidity in terms of diabetes and/or hypertension plus any other disease, four out of five studies were conducted in sub-Saharan Africa and included people with diabetes and/or hypertension (and other NCDs) and HIV. Due to successful transformation of the health systems to deliver HIV programmes, sub-Saharan Africa is presented with a unique opportunity to leverage the investments made in order to scale-up NCD services. This can be achieved in various ways, such as integrating NCD services into facilities originally providing HIV care only, integrating HIV care into PHC facilities that offer NCD care, or concurrent introduction of HIV and NCD services.[8] However, even though this is recognised, there are still questions linked to the implementation of integrated models of care. In South Africa, the ICDM model, the intervention evaluated in the ITS study by Ameh and colleagues,[36] is one example where the vertical HIV programme was integrated into general PHC facilities. As part of the pilot programme, Ameh and colleagues not only evaluated the impact on health outcomes, but also conducted a qualitative study to explore the perspectives of healthcare providers and patients on the quality of care in the ICDM model.[83] They found that PHC facilities experienced BP drug stock-outs, lack of functioning BP machines and staff shortages, among others, which impacted on the delivery of care and indirectly

therefore on the health outcomes. Integrated NCD and HIV care is implemented to a varying degree in other sub-Saharan African countries. A study examining policies and programmes for integrated HIV and NCD care in Malawi, Kenya, South Africa and Swaziland found that these countries still experience challenges in implementing integrated care. Some of these are related to inadequate data to determine the burden of NCDs among PLHIV at a local level, lack of evidence to support the implementation of integrated care models, inadequate stakeholder engagement, lack of NCD care capacity and other health system challenges.[84]

Our definition of integrated care was based on a "one-stop-shop" model whereby a patient receives all necessary care or services under one roof by one or more health-care professional (Figure 1), which is just one way of describing integrated care. Indeed, a narrative review by Njuguna, et al. [85] aimed to describe various models of integrated care for HIV and NCDs in sub-Saharan Africa. Based on the definition by WHO, the authors defined integrated care as the "coordination, co-location, or simultaneous delivery of HIV and NCD services to patients who need it, when they need it" and identified five models. These include community-based integrated HIV and NCD screening in the general population; screening for NCD risk factors among PLHIV; integrated care for HIV and NCDs in healthcare facilities through leveraging the HIV infrastructure to manage NCDs; differential care for people well-controlled HIV or NCDs, which includes longer follow-up periods for stable patients; and population health for all patients with any need.[85] We included two cluster RCTs that aimed to promote integrated care through clinical management tools, which is different from integrated care at facility level. We discussed this within our team and concluded that the aim of these interventions was to provide care in a holistic way and to address all the needs of an individual when s/he presents to a healthcare facility, and thus met our eligibility criteria.

Integration of care for NCDs and HIV or other diseases is complex, partly due to the complex nature of health systems.[86] Our review focused on the effectiveness of integrating care for people with diabetes, hypertension and other co-morbidities in terms of health outcomes, which is just one question that needs to be answered. In other words, the question of our review focused on one building block of health systems as described by the WHO.[86] Although we aimed to examine process outcomes, these were limited to access to care, retention in care, adherence, continuity of care, quality of care and cost of care; and were poorly reported across included studies. The scope of our review did not include outcomes related to implementation or perspectives from health providers and patients, which are important aspects to consider. Although the literature predominantly highlights the need to integrate NCD and HIV care, integrating mental health services into existing NCD and or HIV services is just as important. Four[42-45] of the five ongoing studies that we identified examine integration of mental health with NCDs.

Conclusion

The evidence on the effectiveness of integrated models of care for people with diabetes, hypertension and other co-morbidities, on health outcomes is very uncertain. We therefore do not know whether integrated models of care lead to better or worse outcomes, or may make no difference at all among people with diabetes, hypertension and other chronic conditions. There is a need to scale-up NCD services, particularly in LMICs. In the context of an increasing burden of NCDs against a backdrop of other chronic diseases, and scarce health system resources, such as human capacity and funding, policies and programmes need to promote integrated models of care and holistic, patient-centred services. However, these need to take into consideration context-specific factors related to the health system and the targeted population.

Further rigorous studies assessing the effects of integrated models of care on health outcomes are needed. These studies should include an adequate description of the integrated model of care,

assess long term health effects as well as patient important outcomes, and cost of care. Furthermore, there is a need to conduct implementation research, economic evaluations as well as qualitative research on the barriers and facilitators to integrated models of care at patient and health-system level in order to guide policy makers in planning and allocation of resources in order to maximise the potential benefits of integrated care as well strengthening the health systems in achieving universal health coverage in LMICs.

Authors' contributions

All authors contributed to development of the review protocol. JUN and AR screened titles and abstracts; JUN, AR, TY and CMB participated in full text screening; TY, JJM and IT helped to resolve discrepancies. AR, JUN and IT extracted data and assessed risk of bias. AR and IT assessed certainty of evidence with input from TY and JJM. TY and JJM provided overall methodological guidance. JUN drafted the background section, AR drafted the rest of the manuscript. JUN, IT, TY, and CMB critically read and revised the manuscript. All authors have approved the final version of the manuscript.

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Data sharing statement

Not applicable

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Competing interests statement

All authors have no known conflict of interest.

Protocol

Uwimana Nicol J, Rohwer A, Young T, et al. Integrated models of care for diabetes and hypertension in low- and middle-income countries (LMICs): Protocol for a systematic review. *Syst Rev* 2018;7(1):203. doi: 10.1186/s13643-018-0865-8 [published Online First: 2018/11/22]

Figures

Figure 1: Logic model of integrated care

Figure 2: PRISMA flow diagram

Figure 3: Risk of bias in ITS studies

Figure 4: Risk of bias for cluster RCTs

Supplementary files

Supplementary file 1: MEDLINE (PubMed) search strategy

Supplementary file 2: Summary of interventions according to the TIDiER checklist: Integrated models of care

Supplementary file 3: Summary of interventions according to the TIDiER checklist: Interventions to promote integrated management of care

Supplementary file 4: Risk of bias assessments for included studies

Supplementary file 5: Forest plots

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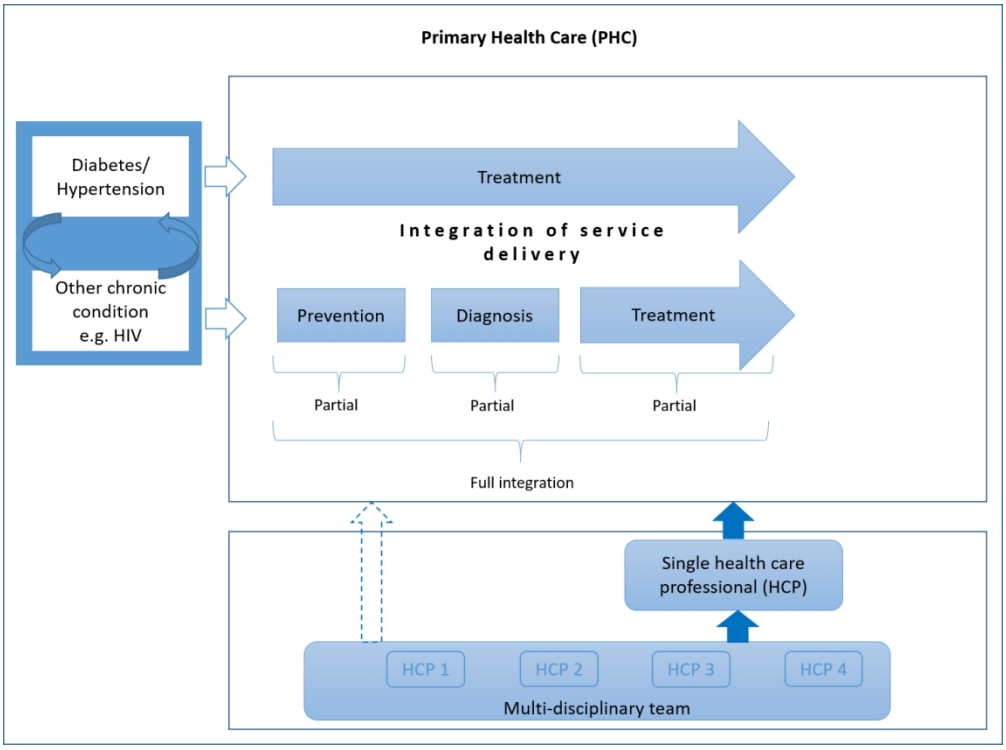


Figure 1: Logic model of integrated care

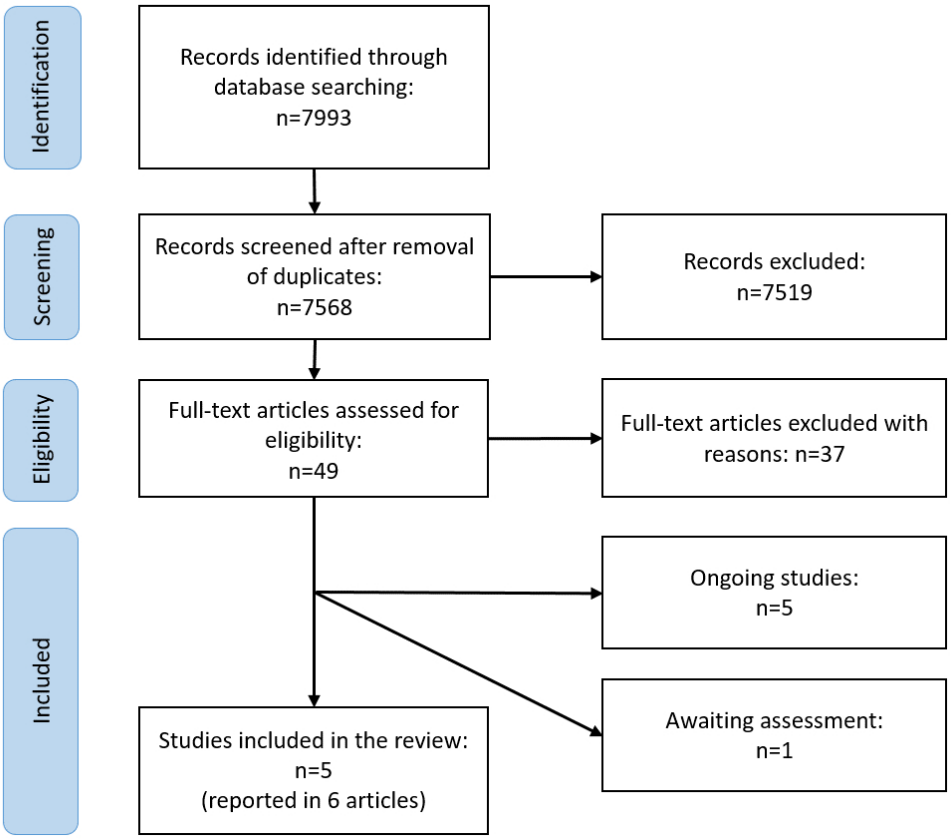


Figure 2: PRISMA flow diagram

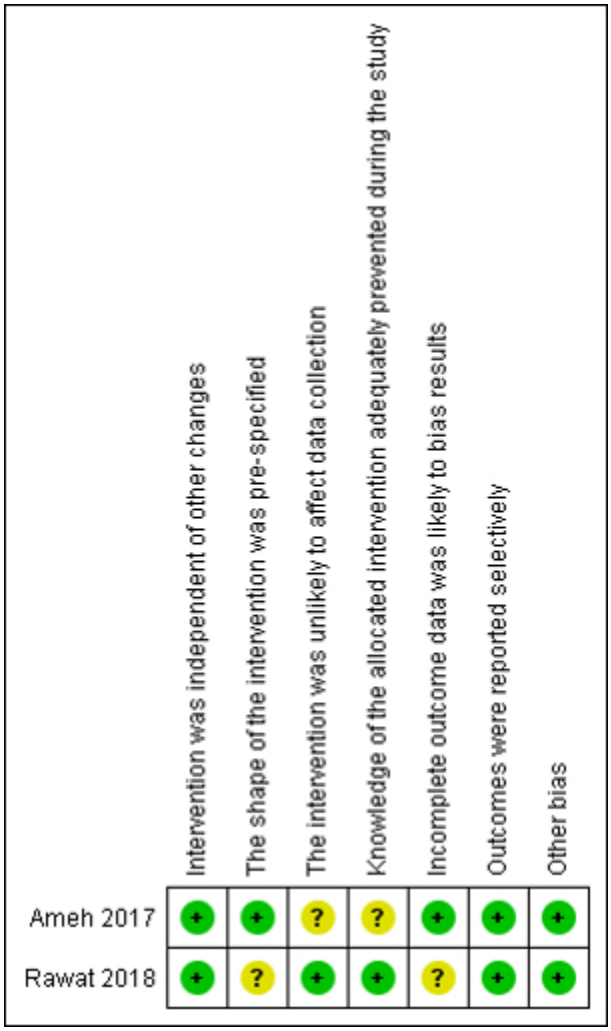


Figure 3: Risk of bias in ITS studies

Figure 4: Risk of bias for cluster RCTs

Supplementary file 1: Medline (PubMed) search strategy

#1 "Hypertension"[Mesh] OR (hypertension OR hypertention OR "blood pressure" OR “arterial pressure” OR systolic OR diastolic)[title/abstract]

#2 diabetes OR "diabetes mellitus")[title/abstract] OR "Diabetes Mellitus"[Mesh])

#3 #1 OR #2

#4 (dyslipidaemia OR dyslipidemia OR cholesterol OR LDL OR HDL OR triglyceride OR triglycerides OR low density lipoprotein OR high density lipoprotein OR low-density lipoprotein OR high-density lipoprotein)[title/abstract] OR "Dyslipidemias"[Mesh]

#5 ((((HIV OR hiv-1 OR hiv-2* OR hiv1 OR hiv2 OR hiv infect* OR human immunodeficiency virus OR human immune deficiency virus OR human immuno-deficiency virus OR human immune-deficiency virus OR ((human immun*) AND (deficiency virus)) OR acquired immunodeficiency syndromes OR acquired immune deficiency syndrome OR acquired immuno-deficiency syndrome OR acquired immune-deficiency syndrome OR ((acquired immun*) AND (deficiency syndrome)) OR HIV/AIDS)))) OR ((HIV infections [MeSH] OR HIV [MeSH]))

#6 (tuberculosis OR tuberculoses OR tb)[Title/Abstract] OR "tuberculosis"[Mesh]

#7 "noncommunicable disease" OR "noncommunicable diseases" OR "non-communicable disease" OR "non-communicable diseases" OR NCD OR NCDs OR "Noncommunicable Diseases"[Mesh]

#8 (comorbid* OR co-morbid* OR "co morbidity" OR multimorbidity OR multi-morbid OR "multi morbidity")[title/abstract] OR "Multimorbidity"[Mesh] OR "Comorbidity"[Mesh]

#9 multi-disease* OR multidisease* OR multi disease* OR multiple condition* OR multi-condition* OR multi condition* OR multiple illness* OR multi-illness* OR multi illness* OR multiple syndrome* OR multi-syndrome* OR multi syndrome* OR concurrent condition* OR concurrent illness* OR concurrent disease* OR co-existing disease* OR coexisting disease* OR co-existing illness* OR coexisting illness* OR co-existing syndrome* OR coexisting syndrome* OR co-existing condition* OR coexisting condition* OR co-occurring disease* OR co occuring disease* OR cooccuring disease* OR co-occurring illness* OR co occurring illness* OR cooccurring illness* OR co-occurring syndrome* OR co occurring syndrome* OR cooccurring syndrome* OR co-occurring condition* OR co occurring condition* OR cooccurring condition*

#10 chronic disease* OR lifestyle disease* OR "diseases of lifestyle" OR "disease of lifestyle" OR "Multiple Chronic Conditions"[Mesh] OR "Chronic Disease"[Mesh]

#11 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

#12 "Delivery of Health Care, Integrated"[Mesh] OR “delivery of care” OR “delivery of health” OR "delivery of healthcare" OR "Comprehensive Health Care"[Mesh] OR "comprehensive healthcare" OR "comprehensive care" OR "comprehensive health" OR "Continuity of Patient Care"[Mesh] OR "continuity of patient care" OR "continuity of care" OR "continuity of health" OR "continuity of healthcare" OR "Patient-Centered Care"[Mesh] OR "patient centered care" OR "patient centred care"

#13 "Referral and Consultation"[Mesh] OR (referral AND consultation)

#14 integrat* care OR "integration of care" OR integrat* services OR "integration of services" OR integrat* programmes OR integrat* programs OR “integration of programmes” OR “integration of programs” OR integrat* service delivery OR “integration of service delivery” OR integrat* services OR “integration of services” OR integrat* delivery OR integrat* management OR “integration of management”

#15 coordinat* care OR "coordination of care" OR coordinat* services OR "coordination of services" OR coordinat* programmes OR coordinat* programs OR “coordination of programmes” OR “coordination of programs” OR coordinat* service delivery OR “coordination of service delivery” OR coordinat* services OR “coordination of services” OR coordinat* delivery OR coordinat* management OR “coordination of management”

#16 co-ordinat* care OR "co-ordination of care" OR co-ordinat* services OR "co-ordination of services" OR co-ordinat* programmes OR co-ordinat* programs OR “co-ordination of programmes” OR “co-ordination of programs” OR co-ordinat* service delivery OR “co-ordination of service delivery” OR co-ordinat* services OR “co-ordination of services” OR co-ordinat* delivery OR co-ordinat* management OR “co-ordination of management”

#17 horizontal care OR vertical care OR horizontal services OR vertical services OR horizontal programmes OR horizontal programs OR vertical programmes OR vertical programs OR horizontal service delivery OR vertical service delivery OR horizontal services OR vertical services OR horizontal delivery OR vertical management OR vertical management

#18 “multi team” OR multiteam “multi care” OR multicare OR “multi clinic” OR multiclinic OR “multi service” OR multiservice OR “multi program” OR multiprogram OR “multi programme” OR “multi delivery” OR multidelivery OR “multi management”

#19 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18

#20 #3 AND #11 AND #19

#21 Developing Countries[Mesh:noexp] OR Africa[Mesh:noexp] OR Africa, Northern[Mesh:noexp] OR Africa South of the Sahara[Mesh:noexp] OR Africa, Central[Mesh:noexp] OR Africa, Eastern[Mesh:noexp] OR Africa, Southern[Mesh:noexp] OR Africa, Western[Mesh:noexp] OR Asia[Mesh:noexp] OR Asia, Central[Mesh:noexp] OR Asia, Southeastern[Mesh:noexp] OR Asia, Western[Mesh:noexp] OR Caribbean Region[Mesh:noexp] OR West Indies[Mesh:noexp] OR South America[Mesh:noexp] OR Latin America[Mesh:noexp] OR Central America[Mesh:noexp] OR Afghanistan[Mesh:noexp] OR Albania[Mesh:noexp] OR Algeria[Mesh:noexp] OR American Samoa[Mesh:noexp] OR Angola[Mesh:noexp] OR "Antigua and Barbuda"[Mesh:noexp] OR Argentina[Mesh:noexp] OR Armenia[Mesh:noexp] OR Azerbaijan[Mesh:noexp] OR Bahrain[Mesh:noexp] OR Bangladesh[Mesh:noexp] OR Barbados[Mesh:noexp] OR Benin[Mesh:noexp] OR Byelarus[Mesh:noexp] OR Belize[Mesh:noexp] OR Bhutan[Mesh:noexp] OR Bolivia[Mesh:noexp] OR Bosnia-Herzegovina[Mesh:noexp] OR Botswana[Mesh:noexp] OR Brazil[Mesh:noexp] OR Bulgaria[Mesh:noexp] OR Burkina Faso[Mesh:noexp] OR Burundi[Mesh:noexp] OR Cambodia[Mesh:noexp] OR Cameroon[Mesh:noexp] OR Cape Verde[Mesh:noexp] OR Central African Republic[Mesh:noexp] OR Chad[Mesh:noexp] OR Chile[Mesh:noexp] OR China[Mesh:noexp] OR Colombia[Mesh:noexp] OR Comoros[Mesh:noexp] OR Congo[Mesh:noexp] OR Costa Rica[Mesh:noexp] OR Cote d'Ivoire[Mesh:noexp] OR Croatia[Mesh:noexp] OR Cuba[Mesh:noexp] OR Cyprus[Mesh:noexp] OR Czechoslovakia[Mesh:noexp] OR Czech Republic[Mesh:noexp] OR Slovakia[Mesh:noexp] OR Djibouti[Mesh:noexp] OR "Democratic Republic of the Congo"[Mesh:noexp] OR Dominica[Mesh:noexp] OR Dominican Republic[Mesh:noexp] OR East Timor[Mesh:noexp] OR Ecuador[Mesh:noexp] OR Egypt[Mesh:noexp] OR El Salvador[Mesh:noexp] OR Eritrea[Mesh:noexp] OR Estonia[Mesh:noexp] OR Ethiopia[Mesh:noexp] OR Fiji[Mesh:noexp] OR Gabon[Mesh:noexp] OR Gambia[Mesh:noexp] OR "Georgia (Republic)"[Mesh:noexp] OR Ghana[Mesh:noexp] OR Greece[Mesh:noexp] OR Grenada[Mesh:noexp] OR Guatemala[Mesh:noexp] OR Guinea[Mesh:noexp] OR Guinea-Bissau[Mesh:noexp] OR Guam[Mesh:noexp] OR Guyana[Mesh:noexp] OR Haiti[Mesh:noexp] OR Honduras[Mesh:noexp] OR Hungary[Mesh:noexp] OR India[Mesh:noexp] OR Indonesia[Mesh:noexp] OR Iran[Mesh:noexp] OR Iraq[Mesh:noexp] OR

Jamaica[Mesh:noexp] OR Jordan[Mesh:noexp] OR Kazakhstan[Mesh:noexp] OR Kenya[Mesh:noexp] OR Korea[Mesh:noexp] OR Kosovo[Mesh:noexp] OR Kyrgyzstan[Mesh:noexp] OR Laos[Mesh:noexp] OR Latvia[Mesh:noexp] OR Lebanon[Mesh:noexp] OR Lesotho[Mesh:noexp] OR Liberia[Mesh:noexp] OR Libya[Mesh:noexp] OR Lithuania[Mesh:noexp] OR Macedonia[Mesh:noexp] OR Madagascar[Mesh:noexp] OR Malaysia[Mesh:noexp] OR Malawi[Mesh:noexp] OR Mali[Mesh:noexp] OR Malta[Mesh:noexp] OR Mauritania[Mesh:noexp] OR Mauritius[Mesh:noexp] OR Mexico[Mesh:noexp] OR Micronesia[Mesh:noexp] OR Middle East[Mesh:noexp] OR Moldova[Mesh:noexp] OR Mongolia[Mesh:noexp] OR Montenegro[Mesh:noexp] OR Morocco[Mesh:noexp] OR Mozambique[Mesh:noexp] OR Myanmar[Mesh:noexp] OR Namibia[Mesh:noexp] OR Nepal[Mesh:noexp] OR Netherlands Antilles[Mesh:noexp] OR New Caledonia[Mesh:noexp] OR Nicaragua[Mesh:noexp] OR Niger[Mesh:noexp] OR Nigeria[Mesh:noexp] OR Oman[Mesh:noexp] OR Pakistan[Mesh:noexp] OR Palau[Mesh:noexp] OR Panama[Mesh:noexp] OR Papua New Guinea[Mesh:noexp] OR Paraguay[Mesh:noexp] OR Peru[Mesh:noexp] OR Philippines[Mesh:noexp] OR Poland[Mesh:noexp] OR Portugal[Mesh:noexp] OR Puerto Rico[Mesh:noexp] OR Romania[Mesh:noexp] OR Russia[Mesh:noexp] OR "Russia (Pre-1917)"[Mesh:noexp] OR Rwanda[Mesh:noexp] OR "Saint Kitts and Nevis"[Mesh:noexp] OR Saint Lucia[Mesh:noexp] OR "Saint Vincent and the Grenadines"[Mesh:noexp] OR Samoa[Mesh:noexp] OR Saudi Arabia[Mesh:noexp] OR Senegal[Mesh:noexp] OR Serbia[Mesh:noexp] OR Montenegro[Mesh:noexp] OR Seychelles[Mesh:noexp] OR Sierra Leone[Mesh:noexp] OR Slovenia[Mesh:noexp] OR Sri Lanka[Mesh:noexp] OR Somalia[Mesh:noexp] OR South Africa[Mesh:noexp] OR Sudan[Mesh:noexp] OR Suriname[Mesh:noexp] OR Swaziland[Mesh:noexp] OR Syria[Mesh:noexp] OR Tajikistan[Mesh:noexp] OR Tanzania[Mesh:noexp] OR Thailand[Mesh:noexp] OR Togo[Mesh:noexp] OR Tonga[Mesh:noexp] OR "Trinidad and Tobago"[Mesh:noexp] OR Tunisia[Mesh:noexp] OR Turkey[Mesh:noexp] OR Turkmenistan[Mesh:noexp] OR Uganda[Mesh:noexp] OR Ukraine[Mesh:noexp] OR Uruguay[Mesh:noexp] OR USSR[Mesh:noexp] OR Uzbekistan[Mesh:noexp] OR Vanuatu[Mesh:noexp] OR Venezuela[Mesh:noexp] OR Vietnam[Mesh:noexp] OR Yemen[Mesh:noexp] OR Yugoslavia[Mesh:noexp] OR Zambia[Mesh:noexp] OR Zimbabwe[Mesh:noexp]

#22 Macedonia[tw] OR Madagascar[tw] OR Malagasy Republic[tw] OR Malaysia[tw] OR Malaya[tw] OR Malay[tw] OR Sabah[tw] OR Sarawak[tw] OR Malawi[tw] OR Nyasaland[tw] OR Mali[tw] OR Malta[tw] OR Marshall Islands[tw] OR Mauritania[tw] OR Mauritius[tw] OR Agalega Islands[tw] OR Mexico[tw] OR Micronesia[tw] OR Middle East[tw] OR Moldova[tw] OR Moldovia[tw] OR Moldovian[tw] OR Mongolia[tw] OR Montenegro[tw] OR Morocco[tw] OR Ifni[tw] OR Mozambique[tw] OR Myanmar[tw] OR Myanma[tw] OR Burma[tw] OR Namibia[tw] OR Nepal[tw] OR Netherlands Antilles[tw] OR New Caledonia[tw] OR Nicaragua[tw] OR Niger[tw] OR Nigeria[tw] OR Northern Mariana Islands[tw] OR Oman[tw] OR Muscat[tw] OR Pakistan[tw] OR Palau[tw] OR Palestine[tw] OR Panama[tw] OR Paraguay[tw] OR Peru[tw] OR Philippines[tw] OR Philipines[tw] OR Phillipines[tw] OR Phillippines[tw] OR Poland[tw] OR Portugal[tw] OR Puerto Rico[tw] OR Romania[tw] OR Rumania[tw] OR Roumania[tw] OR Russia[tw] OR Russian[tw] OR Rwanda[tw] OR Ruanda[tw] OR Saint Kitts[tw] OR St Kitts[tw] OR Nevis[tw] OR Saint Lucia[tw] OR St Lucia[tw] OR Saint Vincent[tw] OR St Vincent[tw] OR Grenadines[tw] OR Samoa[tw] OR Samoan Islands[tw] OR Navigator Island[tw] OR Navigator Islands[tw] OR Sao Tome[tw] OR Saudi Arabia[tw] OR Senegal[tw] OR Serbia[tw] OR Montenegro[tw] OR Seychelles[tw] OR Sierra Leone[tw] OR Slovenia[tw] OR Sri Lanka[tw] OR Ceylon[tw] OR Solomon Islands[tw] OR Somalia[tw] OR Sudan[tw] OR Suriname[tw] OR Surinam[tw] OR Swaziland[tw] OR Syria[tw] OR Tajikistan[tw] OR Tadzhikistan[tw] OR Tadjikistan[tw] OR Tadzhik[tw] OR Tanzania[tw] OR Thailand[tw] OR Togo[tw] OR Togolese Republic[tw] OR Tonga[tw] OR Trinidad[tw] OR Tobago[tw] OR Tunisia[tw] OR Turkey[tw] OR Turkmenistan[tw] OR Turkmen[tw] OR Uganda[tw] OR Ukraine[tw] OR Uruguay[tw] OR USSR[tw] OR Soviet Union[tw] OR Union of Soviet Socialist Republics[tw] OR Uzbekistan[tw] OR Uzbek OR Vanuatu[tw] OR New

Hebrides[tw] OR Venezuela[tw] OR Vietnam[tw] OR Viet Nam[tw] OR West Bank[tw] OR Yemen[tw] OR Yugoslavia[tw] OR Zambia[tw] OR Zimbabwe[tw] OR Rhodesia[tw]

#23 Africa[tw] OR Asia[tw] OR Caribbean[tw] OR West Indies[tw] OR South America[tw] OR Latin America[tw] OR Central America[tw] OR Afghanistan[tw] OR Albania[tw] OR Algeria[tw] OR Angola[tw] OR Antigua[tw] OR Barbuda[tw] OR Argentina[tw] OR Armenia[tw] OR Armenian[tw] OR Aruba[tw] OR Azerbaijan[tw] OR Bahrain[tw] OR Bangladesh[tw] OR Barbados[tw] OR Benin[tw] OR Byelarus[tw] OR Byelorussian[tw] OR Belarus[tw] OR Belorussian[tw] OR Belorussia[tw] OR Belize[tw] OR Bhutan[tw] OR Bolivia[tw] OR Bosnia[tw] OR Herzegovina[tw] OR Hercegovina[tw] OR Botswana[tw] OR Brasil[tw] OR Brazil[tw] OR Bulgaria[tw] OR Burkina Faso[tw] OR Burkina Fasso[tw] OR Upper Volta[tw] OR Burundi[tw] OR Urundi[tw] OR Cambodia[tw] OR Khmer Republic[tw] OR Kampuchea[tw] OR Cameroon[tw] OR Cameroons[tw] OR Cameron[tw] OR Camerons[tw] OR Cape Verde[tw] OR Central African Republic[tw] OR Chad[tw] OR Chile[tw] OR China[tw] OR Colombia[tw] OR Comoros[tw] OR Comoro Islands[tw] OR Comores[tw] OR Mayotte[tw] OR Congo[tw] OR Zaire[tw] OR Costa Rica[tw] OR Cote d'Ivoire[tw] OR Ivory Coast[tw] OR Croatia[tw] OR Cuba[tw] OR Cyprus[tw] OR Czechoslovakia[tw] OR Czech Republic[tw] OR Slovakia[tw] OR Slovak Republic[tw] OR Djibouti[tw] OR French Somaliland[tw] OR Dominica[tw] OR Dominican Republic[tw] OR East Timor[tw] OR East Timur[tw] OR Timor Leste[tw] OR Ecuador[tw] OR Egypt[tw] OR United Arab Republic[tw] OR El Salvador[tw] OR Eritrea[tw] OR Estonia[tw] OR Ethiopia[tw] OR Fiji[tw] OR Gabon[tw] OR Gabonese Republic[tw] OR Gambia[tw] OR Gaza[tw] OR Georgia Republic[tw] OR Georgian Republic[tw] OR Ghana[tw] OR Gold Coast[tw] OR Greece[tw] OR Grenada[tw] OR Guatemala[tw] OR Guinea[tw] OR Guam[tw] OR Guiana[tw] OR Guyana[tw] OR Haiti[tw] OR Honduras[tw] OR Hungary[tw] OR India[tw] OR Maldives[tw] OR Indonesia[tw] OR Iran[tw] OR Iraq[tw] OR Isle of Man[tw] OR Jamaica[tw] OR Jordan[tw] OR Kazakhstan[tw] OR Kazakh[tw] OR Kenya[tw] OR Kiribati[tw] OR Korea[tw] OR Kosovo[tw] OR Kyrgyzstan[tw] OR Kirghizia[tw] OR Kyrgyz Republic[tw] OR Kirghiz[tw] OR Kirgizstan[tw] OR "Lao PDR"[tw] OR Laos[tw] OR Latvia[tw] OR Lebanon[tw] OR Lesotho[tw] OR Basutoland[tw] OR Liberia[tw] OR Libya[tw] OR Lithuania[tw]

#24 "developing country"[tw] OR "developing countries"[tw] OR "developing nation"[tw] OR "developing nations"[tw] OR "developing population"[tw] OR "developing populations"[tw] OR "developing world"[tw] OR "less developed country"[tw] OR "less developed countries"[tw] OR "less developed nation"[tw] OR "less developed nations"[tw] OR "less developed population"[tw] OR "less developed populations"[tw] OR "less developed world"[tw] OR "lesser developed country"[tw] OR "lesser developed countries"[tw] OR "lesser developed nation"[tw] OR "lesser developed nations"[tw] OR "lesser developed population"[tw] OR "lesser developed populations"[tw] OR "lesser developed world"[tw] OR "under developed country"[tw] OR "under developed countries"[tw] OR "under developed nation"[tw] OR "under developed nations"[tw] OR "under developed population"[tw] OR "under developed populations"[tw] OR "under developed world"[tw] OR "underdeveloped country"[tw] OR "underdeveloped countries"[tw] OR "underdeveloped nation"[tw] OR "underdeveloped nations"[tw] OR "underdeveloped population"[tw] OR "underdeveloped populations"[tw] OR "underdeveloped world"[tw] OR "middle income country"[tw] OR "middle income countries"[tw] OR "middle income nation"[tw] OR "middle income nations"[tw] OR "middle income population"[tw] OR "middle income populations"[tw] OR "low income country"[tw] OR "low income countries"[tw] OR "low income nation"[tw] OR "low income nations"[tw] OR "low income population"[tw] OR "low income populations"[tw] OR "lower income country"[tw] OR "lower income countries"[tw] OR "lower income nation"[tw] OR "lower income nations"[tw] OR "lower income population"[tw] OR "lower income populations"[tw] OR "underserved country"[tw] OR "underserved countries"[tw] OR "underserved nation"[tw] OR "underserved nations"[tw] OR "underserved population"[tw] OR "underserved populations"[tw] OR "underserved world"[tw] OR "under served country"[tw] OR "under served countries"[tw] OR "under served nation"[tw] OR "under served nations"[tw] OR "under served population"[tw] OR "under served populations"[tw] OR "under served

world"[tw] OR "deprived country"[tw] OR "deprived countries"[tw] OR "deprived nation"[tw] OR "deprived nations"[tw] OR "deprived population"[tw] OR "deprived populations"[tw] OR "deprived world"[tw] OR "poor country"[tw] OR "poor countries"[tw] OR "poor nation"[tw] OR "poor nations"[tw] OR "poor population"[tw] OR "poor populations"[tw] OR "poor world"[tw] OR "poorer country"[tw] OR "poorer countries"[tw] OR "poorer nation"[tw] OR "poorer nations"[tw] OR "poorer population"[tw] OR "poorer populations"[tw] OR "poorer world"[tw] OR "developing economy"[tw] OR "developing economies"[tw] OR "less developed economy"[tw] OR "less developed economies"[tw] OR "lesser developed economy"[tw] OR "lesser developed economies"[tw] OR "under developed economy"[tw] OR "under developed economies"[tw] OR "underdeveloped economy"[tw] OR "underdeveloped economies"[tw] OR "middle income economy"[tw] OR "middle income economies"[tw] OR "low income economy"[tw] OR "low income economies"[tw] OR "lower income economy"[tw] OR "lower income economies"[tw] OR "low gdp"[tw] OR "low gnp"[tw] OR "low gross domestic"[tw] OR "low gross national"[tw] OR "lower gdp"[tw] OR "lower gnp"[tw] OR "lower gross domestic"[tw] OR "lower gross national"[tw] OR lmic[tw] OR lmics[tw] OR "third world"[tw] OR "lami country"[tw] OR "lami countries"[tw] OR "transitional country"[tw] OR "transitional countries"[tw]

#25 #21 OR #22 OR #23 OR #24

#26 #20 AND #25

Supplementary file 2: Summary of interventions according to the TIDiER checklist: Integrated models of care

Study ID	**Ameh 2017**		**Rawat 2018***	**Havlir 2019**	
Intervention groups	**Intervention**	**Control**	**Intervention**	**Intervention**	**Control**
Name of intervention	Integrated chronic disease management (ICDM) model	Standard care in clinics where ICDM model was not piloted	Implementation of national policy to integrate HIV care into all PHC facilities	Integrated care: Baseline HIV and multi-disease testing plus annual testing, universal ART and patient-centered care	Usual care: Baseline HIV and multi-disease testing and national guideline-restricted ART, hypertension and diabetes care as per country standard of care
Aim of the intervention	To improve management of patients with HIV, TB, hypertension, diabetes, COPD, asthma, epilepsy and mental health conditions at PHCs	Not reported	To provide comprehensive HIV care (prevention, diagnosis, treatment initiation and follow-up) at PHC facilities	To remove patient-level barriers and maximise the efficiency of the health system To overcome barriers of universal access to HIV treatment and to be able to reach UNAIDS goals	Not reported
Physical and informational materials used	Not reported	Not reported	Not reported	Treatment guidelines ART tablets SMS reminders	National treatment guidelines
Procedures, activities and processes used in the intervention	Facility reorganisation: designated chronic care area; supply of critical medicines; pre-packaging of medication	Not reported	Policy to integrate HIV care into PHC clinics Training of nurses in comprehensive management of HIV: Nurse initiated	Community health campaigns (CHCs): Multi-disease testing for HIV, diabetes and hypertension; counselling and clinic appointments for participants with positive tests; HIV	Community health campaigns: Multi-disease testing for HIV, diabetes and hypertension; counselling and clinic appointments for participants with positive tests; HIV positive

	Clinical management support: use of guidelines to manage chronic diseases (PC101); human resources audit; capacity building; appropriate referral Ward-based outreach teams to ensure individual responsibility and "assisted" self-management Health promotion and population screening		Management of ART (NIMART) Training of nurses through the Practical Approach to Lung Health in South Africa (PALSA PLUS) Additional staff to strengthen drug delivery systems	positive participants received blood tests (CD4, t-cell count, HIV/RNA levels) and one-time round trip transportation voucher for first clinic visit Home-based testing for participants that did not attend CHCs Linkage to ART: HIV positive participants not on ART received appointments to initiate ART within a maximum of 7 days; clinic staff introduced themselves in person or by mobile phone; participants could contact hotline via phone or text message for questions or support; phone/SMS reminders about clinic visits Patient-centered care for HIV, diabetes, hypertension: 3-month visit intervals; flexible clinic hours; reduced waiting time at clinics; welcoming staff; ART to	participants received blood tests (CD4, t-cell count, HIV/RNA levels) and one-time round trip transportation voucher for first clinic visit ART, diabetes and hypertension treatment: provided in accordance with national guidelines

				all HIV positive participants; if not eligible for ART according to national guidelines, trial provided Truvada; hypertension and diabetes treated according to standard algorithms	
Who provided the intervention	Nurses	Nurses	Nurses	CHCs: Study team in collaboration with the local health units and the Ministry of Health in Uganda and Kenya Patient-centered care: government clinics augmented by trial staff	CHCs: Study team in collaboration with the local health units and the Ministry of Health in Uganda and Kenya Care in clinics: Clinic staff, augmented by additional staff funded by trial to mitigate staff shortages
Modes of delivery	Not reported	Not reported	Practical implementation of policy varied across clinics: Either disease-specific nurses in separate consulting rooms (co-location), or one nurse that provided comprehensive care for all diseases in single consultation room	Face-to-face, via telephone or text message	Face-to-face

Location of the intervention	Primary healthcare facilities	Primary healthcare facilities	Primary healthcare clinics: 37 urban clinics 65 rural clinics 30 clinics from former homeland	CHCs: Under large tents in all communities, or home-based Patient-centered care: At clinics	CHC: Under large tents in all communities, or home-based ART, diabetes, hypertension care: At clinics
When and how much the intervention was delivered	Unstable HIV and hypertension patients: follow-up every month Stable HIV and hypertension patients: follow=up every 2-3 months Routine referral of all patients to doctor: Every 6 months	Not reported	Not reported	CHCs: lasted 2 weeks at baseline, annually and at 3 year endpoint during weekdays, evenings and weekends Clinic visits: 3-month intervals	CHCs: lasted 2 weeks at baseline and at 3 year endpoint during weekdays, evenings and weekends Clinic visits: not reported
Tailoring of the intervention	Not reported	Not reported	Modular structures and pharmacy renovations to address space concerns in some clinics	Not reported	Not reported
Modifications of the intervention	Not reported	Not reported	Not reported	The end point of the trial was reduced from 5 years to 3 years	Control clinics implemented ART guidelines that were specific to Uganda and Kenya; during the trial, the threshold for eligibility for ART in these countries expanded from a specific CD4+ T-cell count (ranging from <350

					to <500) to universal treatment (regardless of CD4+ T-cell count)
Assessment of intervention adherence/fidelity	Not reported	Not reported	Not reported	Not reported	Not reported
Intervention delivered as planned	Not reported	Not reported	Not reported	Not reported	Not reported

*No control intervention described

HIV human immunodeficiency virus, TB tuberculosis, COPD chronic obstructive pulmonary disease, PHC primary healthcare clinics

Supplementary file 3: Summary of interventions according to the TIDiER checklist: Interventions to promote integrated management of care

Study ID	**Fairall 2016**		**Prabhakaran 2018**	
Intervention groups	**Intervention**	**Control**	**Intervention**	**Control**
Name of intervention	Primary Care (PC) 101	Usual care in for non-communicable and communicable diseases: Practical Approach to Lung Health and HIV/AIDS in South Africa (PALSA PLUS)	mWellcare	Enhanced usual care
Aim of the intervention	To provide comprehensive care for all symptoms, including NCDs, HIV, TB, mental health conditions, women's health	To provide a user-friendly management tool that integrates and harmonises disease-specific guidelines and presents them in a simple format, aligned with patient presentation in primary health care settings, expanded nurses' scope of practice and prescribing (not covering all NCDs)	To facilitate integrated management of hypertension, diabetes, comorbid depression, and alcohol and tobacco use	Not reported
Physical and informational materials used	PC 101 guideline: a 101-page clinical management tool in form of a ring-bound, colour illustrated booklet Desk pads with key messages for priority conditions to facilitate booking of follow-up appointments	Latest version (2011/2012) of PALSA PLUS: clinical management tool	mWellcare system: m-Health-based electronic decision-support system that generates recommendations based on patient profile and risk level, used on Android tablet Visible charts on the management of the conditions	Nurses received a tablet to collect baseline data (without the mWellcare system) Visible charts on the management of the conditions Pamphlets containing lifestyle advice

			Pamphlets containing lifestyle advice	
Procedures, activities and processes used in the intervention	Training of facility trainers Educational outreach sessions by facility trainers Expanded prescribing provisions for nurses Letters and SMS reminders of follow-up visits Financial compensation for patients (voucher for local grocery store) for travel costs and time	Training of facility trainers Educational outreach sessions by facility trainers Financial compensation for patients (voucher for local grocery store) for travel costs and time	Training of physicians on current clinical management guidelines and orientation to mWellcare system Training of nurses in management of hypertension, diabetes, depression, and tobacco and alcohol use Onsite supervision and support SMS reminders of follow-up visits and medication adherence	Training of physicians on clinical management guidelines for hypertension and diabetes Training of NCD nurses in management of hypertension and diabetes mellitus
Who provided the intervention	Training of facility trainers: Experienced adult education practitioner with a background in nursing, family physician who lead the expansion of the clinical management tool Educational outreach sessions: Nurse trainers Care: Nurses	Training of facility trainers: not reported Educational outreach sessions: Nurse trainers Care: Nurses	Training: Study authors Care: NCD nurses and physicians	Training: Study authors Care: NCD nurses and physicians

Modes of delivery	Training and educational outreach sessions: face-to-face Care: Using PC 101 to guide management, details not reported	Training and educational outreach sessions: face-to-face Care: Using PALSA PLUS to guide management, details not reported	All training: face-to-face Care: Patient baseline data entered into mWellcare system which generated a decision support recommendation, lifestyle advice and suggested date for follow-up (printout). The recommendation was reviewed by the physician. Any changes to the recommended plan we captured in the mWellcare system. The nurse provided lifestyle advice and pamphlets	All training: face-to-face Care: According to clinical judgement of physician. Nurses provided and explained pamphlets on lifestyle advice
Location of the intervention	In primary healthcare clinics	In primary healthcare clinics	Community Health Centres	Community Health Centres
When and how much the intervention was delivered	Training of facility trainers: 5-days, in May 2011 and quarterly 1-day workshops Educational outreach sessions: Total of 155 educational outreach sessions, 8 sessions lasting 90 minutes at each of the 19 intervention clinics Care: Stable patients are seen by the nurse every 3-6 months	Educational outreach sessions: 90 minute sessions Follow-up sessions every year Distribution of updated tool every year Care: Stable patients are seen by the nurse every 3-6 months	Training for nurses using the mWellcare system: 3 days Onsite supervision: 2 days Care: follow-up visits according to the recommendation provided by the mWellcare system	Not reported Care: follow-up visits according to the discretion of the physician
Tailoring of the intervention	Not reported	Not reported	Not reported	Not reported

Modifications of the intervention	Unexpected co-intervention by the district department of health: "Chronic Disease Season" (3 month campaign), to improve NCD recognition and care, focusing on diabetes and hypertension, at clinic and community-level. In the community, free screening of blood pressure and glucose levels were offered in public spaces such as shopping centres. People with high values were referred to the clinic. Training of 33 community health workers to provide basic education on diet and lifestyle Facilitated group session to resolve tensions between nurses, doctors and pharmacists related to expanded prescribing provisions	Unexpected co-intervention by the district department of health: "Chronic Disease Season" (3 month campaign), to improve NCD recognition and care, focusing on diabetes and hypertension, at clinic and community-level. In the community, free screening of blood pressure and glucose levels were offered in public spaces such as shopping centres. People with high values were referred to the clinic. Training of 33 community health workers to provide basic education on diet and lifestyle	None reported	None reported
Assessment of intervention adherence/fidelity	Nurse trainers were observed during 5-day workshop and quarterly 1-day workshops Two nurse trainers were interviewed and focus group discussions were held in four intervention clinics in December 2011	Not reported	Monthly visits to all sites by field coordinators who complete a checklist on: intervention delivery, source documents examination, protocol adherence and recording of adverse events	Monthly visits to all sites by field coordinators who complete a checklist on: intervention delivery, source documents examination, protocol adherence and recording of adverse events

			Site visits by investigators: to monitor enrolment process, intervention delivery and protocol adherence	Site visits by investigators: to monitor enrolment process, intervention delivery and protocol adherence
Intervention delivered as planned	Good uptake of nurse trainers, who completed all outreach sessions, and repeated some sessions to ensure that most staff could attend Due to absenteeism and shifts, not all nurses attended all the outreach sessions. In total, 18 nurses attended a median of six training sessions, five pharmacists and four doctors were trained Some variations in the uptake of the PC 101 tool were observed	By 2011, 70% of nurses working in the relevant districts had received training in PALSA PLUS.	Not reported	Not reported

Supplementary file 4: Risk of bias assessments for included studies

Prabhakaran 2018

Domain	Risk of bias	Support for judgement
Random sequence generation *(selection bias)*	**Low risk**	"An independent biostatistician performed central computer-based randomization of CHCs stratified by states (Haryana and Karnataka) and within each state by the availability of NCD nurses recruited under NPCDCS." "using block randomisation (with a block size of 2)"
Allocation concealment *(selection bias)*	**Low risk**	Unit of allocation was an institution. Allocation performed on all units at the start of the study.
Baseline outcome measurements similar	**Low risk**	Measurement of outcomes was conducted in a standardised way. Outcomes were pre-defined and subjective
Baseline characteristics similar	**Low risk**	The EUC arm had a higher proportion of participants with peripheral vascular disease (4.4% versus 0.3%), self-reported tobacco use (17.5% versus 10.0%) and alcohol use (12.3% versus 7.8%), and higher mean SBP (157.0 mm Hg versus 152.5 mm Hg). Outcome measures adjusted for relevant baseline characteristics.
Incomplete outcome data	**Low risk**	No incomplete outcome data suspected. Number of participants in whom the outcomes were assessed were mentioned in a general manner.
Blinding of participants and personnel *(performance bias)*	**High risk**	**Outcome group: All/** "Given the nature of the cluster-randomized trial design, neither personnel nor participants were blinded to the intervention."
Blinding of outcome assessment *(detection bias)*	**Unclear**	**Outcome group: All/** "Assessments at study end were carried out by independent outcome assessors" "It was difficult to blind independent assessors who carried out the end-of-study evaluations"
Protection against contamination	**Low risk**	**Outcome group: All/** low possibility of contamination across clusters
Selective Outcome reporting	**Low risk**	Data on cost-effectiveness mentioned in protocol but not reported in full report of the study, because primary outcome do not differ substantially, otherwise all primary and secondary outcomes reported
Recruitment bias *(e.g. individuals are recruited to the trial after the clusters have been randomized)*	**Unclear**	Patients were recruited after randomisation. Of eligible participants, n=165 in the intervention group and n=193 in the control group were not enrolled in the trial.
Baseline differences clusters	**Unclear**	Characteristics of cluster not described
Loss of clusters	**Low risk**	No loss of clusters reported
Incorrect analysis	Low **risk**	Adjusted for clustering
Comparability *(with RCTs randomised by individuals)*	**Low risk**	No similar studies randomised by individuals found in our search.

Fairall 2016

Domain	Risk of bias	Support for judgement
Random sequence generation *(selection bias)*	**Low risk**	"Randomisation was completed by the trial statistician using nQuery Advisor after recruitment of clinics, independently of the managers giving permission for the clinics to be included in the trial, and prior to patient recruitment and implementation of the intervention."
Allocation concealment *(selection bias)*	**Low risk**	Unit of allocation was an institution. Allocation performed on all units at the start of the study. "Randomisation was completed by the trial statistician using nQuery Advisor after recruitment of clinics, independently of the managers giving permission for the clinics to be included in the trial, and prior to patient recruitment and implementation of the intervention"
Baseline outcome measurements similar	**Low risk**	No differences between groups reported: Baseline BP and HbA1C similar
Baseline characteristics similar	**Unclear**	Baseline characteristics seem similar, but no statistical tests reported
Incomplete outcome data	**Low risk**	Loss to follow-up similar across groups and less than 20%
Blinding of participants and personnel *(performance bias)*	**High risk**	**Outcome group: All** **"Blinding of the intervention was not possible at the clinic level due to the nature of the intervention"**
Blinding of outcome assessment *(detection bias)*	**Unclear**	**Outcome group: All** No blinding of outcome assessors reported Outcome assessors not blinded. This might have influenced BP readings, but not HbA1C (blood test)
Protection against contamination	**Unclear**	**Outcome group: All** Contamination of study arms unlikely. Control clinics might have had access to the guidelines although cluster randomisation took place
Selective Outcome reporting	**Low risk**	**No selective outcome reporting suspected, all** outcomes **listed in the methods section are also** reported **in the results section** – All pre-specified outcomes listed in the trial registration record reported on
Recruitment bias	**Low risk**	"Randomisation was completed by the trial statistician using nQuery Advisor after recruitment of clinics, independently of the managers giving permission for the clinics to be included in the trial, and prior to patient recruitment and implementation of the intervention" All patients were enrolled after the clusters were randomised. However, all eligible patients were included in the study.
Baseline differences (clusters)	**Low risk**	Control clinics had more nurses per clinic and more pharmacies on site compared to the intervention group, but patient load was also higher in the control clinics. Ratio of nurses to patients was similar in both groups
Loss of clusters	**Low risk**	All clinics completed the trial
Incorrect analysis	**Low risk**	Analysis conducted on individual level, but results adjusted for cluster effects. "The cluster randomisation design was accounted for using robust cluster variance-covariance estimates."
Compatibility *(with RCTs randomised by individuals)*	**Low risk**	No similar studies randomised by individuals found in our search
Other bias	**Unclear**	"Midway through the trial, the district health department launched a 3-mo campaign called Chronic Disease Season in all clinics to improve NCD recognition and care. Chronic Disease Season focused on hypertension and diabetes and involved both community and clinic health workers. The community-level interventions included several [a]health screening days[o] in which free blood pressure and finger-prick glucose measurements were offered at venues such as shopping centres and town halls" (Page 7, end)

Havlir 2019

Domain	Risk of bias	Support for judgement
Random sequence generation (selection bias)	**Low risk**	Adequate method – mix of methods used, including computer generated, coin tossing and drawing of lots See description in protocol (p45 version 2.0 (Nov 2012)
Allocation concealment (selection bias)	**Low risk**	Communities were matched and randomised within each pair. Method adequate to not be able to predict allocation
Baseline outcome measurements similar	**Unclear**	No baseline outcome measurements for HIV and hypertension control Page 25, online supplement to article
Baseline characteristics similar	**Low risk**	No obvious difference observed
Incomplete outcome data	**Unclear**	Unclear for HIV and Hypertension cohort, not clear how many at baseline.
Blinding of participants and personnel (performance bias)	**High risk**	No blinding of participants and personnel due to the nature of the intervention. Can influence behaviour of both participants and personnel
Blinding of outcome assessment (detection bias)	**Unclear**	Not reported
Protection against contamination	**Unclear**	Distance from other potential trial communities taken into consideration as part of the eligibility criteria. Migration in and out of communities
Selective Outcome reporting	**Unclear**	Not clear whether dual control of HIV and Hypertension/NCDS was pre-specified
Recruitment bias	**Low risk**	Communities were recruited (selected) before randomisation. Participants were recruited after randomisation, but a household census and Community health campaigns to reach most people in community
Baseline differences (clusters)	**Unclear**	No description of clusters, but cluster pairs were matched for randomisation
Loss of clusters	**Low risk**	No loss of clusters
Incorrect analysis	**Unclear**	Not clear whether adequately adjusted for clustering
Compatibility (with RCTs randomised by individuals)	**Low risk**	No similar studies using individual randomisation found in our search
Other bias	**Unclear**	Primary endpoint should have been 5-year cumulative HIV incidence, but this was shortened to 3 years as the WHO recommendation on ART therapy changed

Rawat 2018

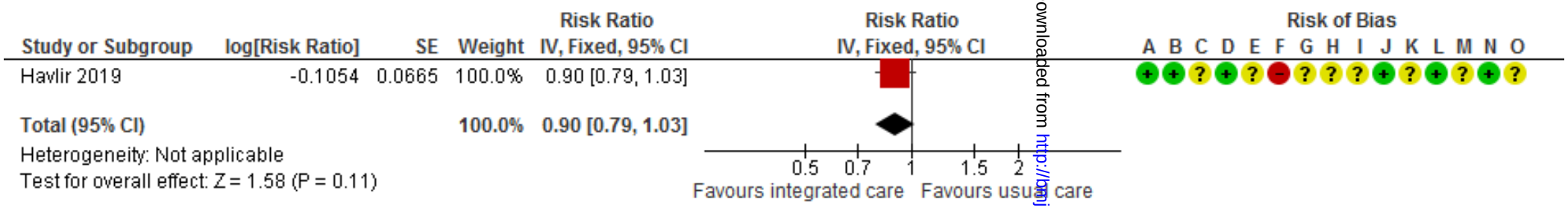
Domain	Risk of bias	Support for judgement
Intervention was independent of other changes	**Low risk**	No other intervention identified. Also, clinics were excluded if they were identified as 'priority sites' that were specifically designed to deliver ART.
The shape of the intervention effect was pre-specified	**High risk**	The shape of the intervention effect was not pre-specified.
The intervention was unlikely to affect data collections	**Low risk**	Data was collected from TIER.net (3 interlinked electronic registers) and the District Health Information System (DHIS) for data collected before and after the intervention.
Knowledge of the allocated intervention *(adequately prevented during the study)*	**Low risk**	Outcomes were based on indicators monitored by the Free State Department of Health. All outcomes are objective
Incomplete outcome data was likely to bias results	**Unclear**	Post-intervention data for diabetes outcomes only available for 18 months post intervention. For other outcomes there is data for 30 months.
Outcomes were reported selectively	**Low risk**	All outcomes reported in the methods section were reported in the results section
Other risks of bias	**Low risk**	No other risks of bias identified. As integration took place at various intervals, seasonality assumed not to have an effect.

Ameh 2017

Domain	Risk of bias	Support for judgement
Intervention was independent of other changes	**Low risk**	No other changes reported.
The shape of the intervention effect was pre-specified	**Low risk**	Point of analysis is the point of intervention
The intervention was unlikely to affect data collections	**Unclear**	It can be assumed that the re-organisation of care delivery also affected data collection in the intervention facilities
Knowledge of the allocated intervention *(adequately prevented during the study)*	**Unclear**	Knowledge of the allocated intervention hard to conceal because of an apparent change in care delivery. Outcomes were not assessed blindly.
Incomplete outcome data was likely to bias results	**Low risk**	No incomplete outcome data suspected. No attrition or missing cases reported, only data for diabetes patients was not reported because there were too few cases (n=4)
Outcomes were reported selectively	**Low risk**	No selective outcome reporting suspected. All outcomes reported in the methods section are reported in the results section
Other risk of bias	**Low risk**	No other sources of bias identified

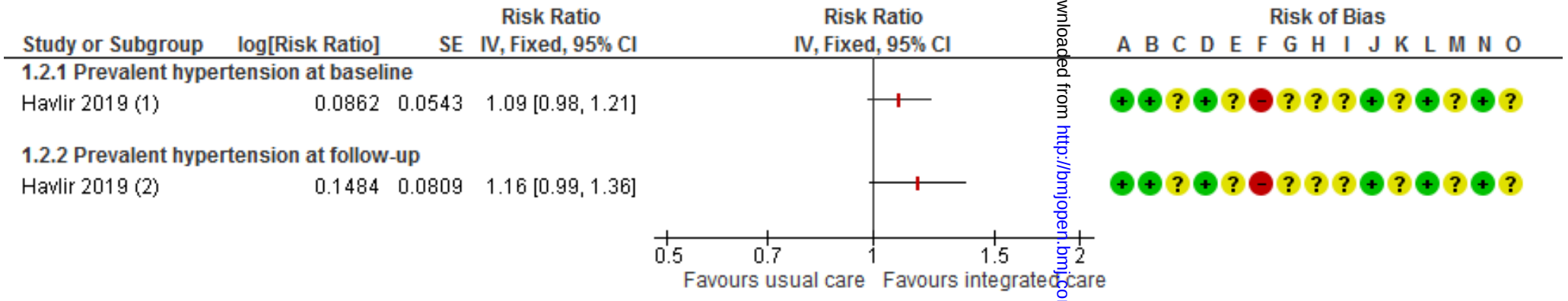
Supplementary file 5: Forest plots

Comparison 1: Integrated models of care vs. usual care
Outcome: Mortality



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Baseline outcome measurements similar
(D) Baseline characteristics similar
(E) Incomplete outcome data (attrition bias)
(F) Blinding of participants and personnel (performance bias)
(G) Blinding of outcome assessment (detection bias)
(H) Protection against contamination
(I) Selective reporting (reporting bias)
(J) Recruitment bias
(K) Baseline differences (clusters)
(L) Loss of clusters
(M) Incorrect analysis
(N) Compatibility with RCTs randomised by individuals
(O) Other bias

Comparison 1: Integrated models of care vs. usual care
Outcome: BP control



Footnotes

(1) Among people living with HIV (PLHIV)

(2) Among people living with HIV (PLHIV)

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Baseline outcome measurements similar

(D) Baseline characteristics similar

(E) Incomplete outcome data (attrition bias)

(F) Blinding of participants and personnel (performance bias)

(G) Blinding of outcome assessment (detection bias)

(H) Protection against contamination

(I) Selective reporting (reporting bias)

(J) Recruitment bias

(K) Baseline differences (clusters)

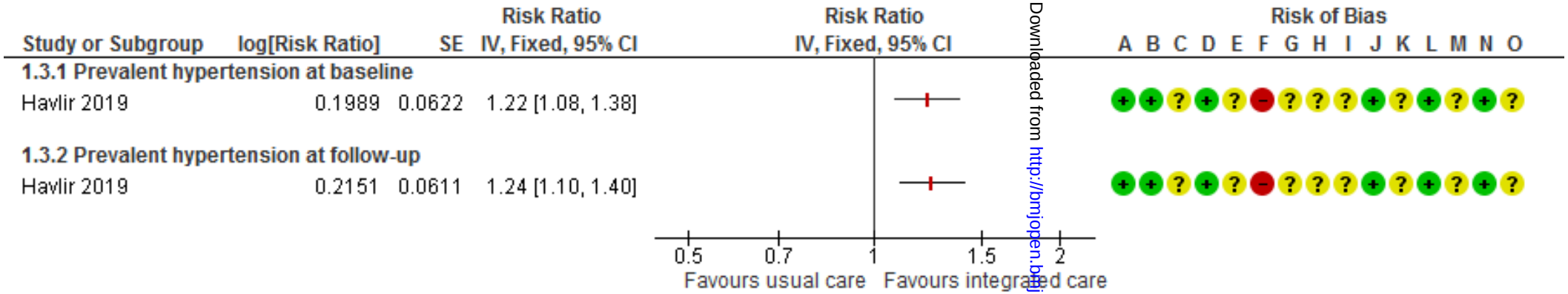
(L) Loss of clusters

(M) Incorrect analysis

(N) Compatibility with RCTs randomised by individuals

(O) Other bias

Comparison 1: Integrated models of care vs. usual care
Outcome: BP and HIV control



Risk of bias legend

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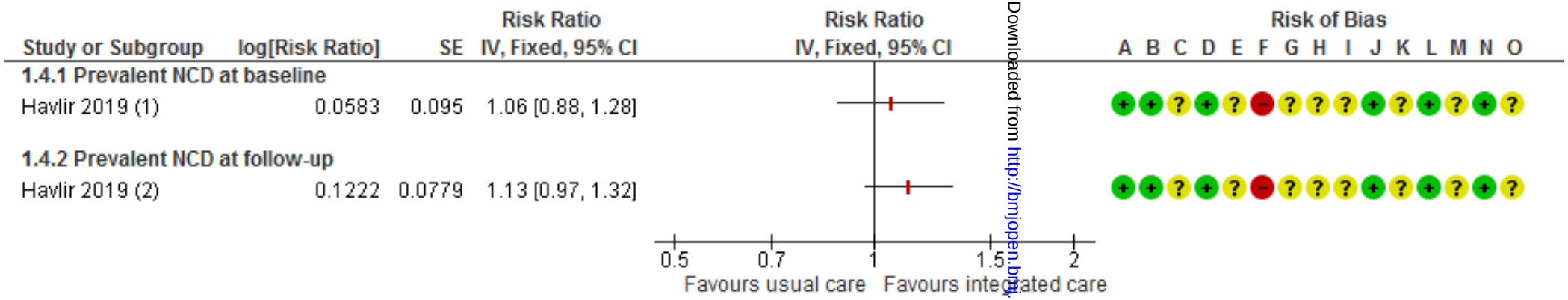
(B) Allocation concealment (selection bias)
(C) Baseline outcome measurements similar
(D) Baseline characteristics similar
(E) Incomplete outcome data (attrition bias)
(F) Blinding of participants and personnel (performance bias)
(G) Blinding of outcome assessment (detection bias)
(H) Protection against contamination
(I) Selective reporting (reporting bias)
(J) Recruitment bias
(K) Baseline differences (clusters)
(L) Loss of clusters
(M) Incorrect analysis
(N) Compatibility with RCTs randomised by individuals
(O) Other bias

Comparison 1: Integrated models of care vs. usual care
Outcome: NCD control



Footnotes
(1) Among PLHIV
(2) Among PLHIV

Risk of bias legend
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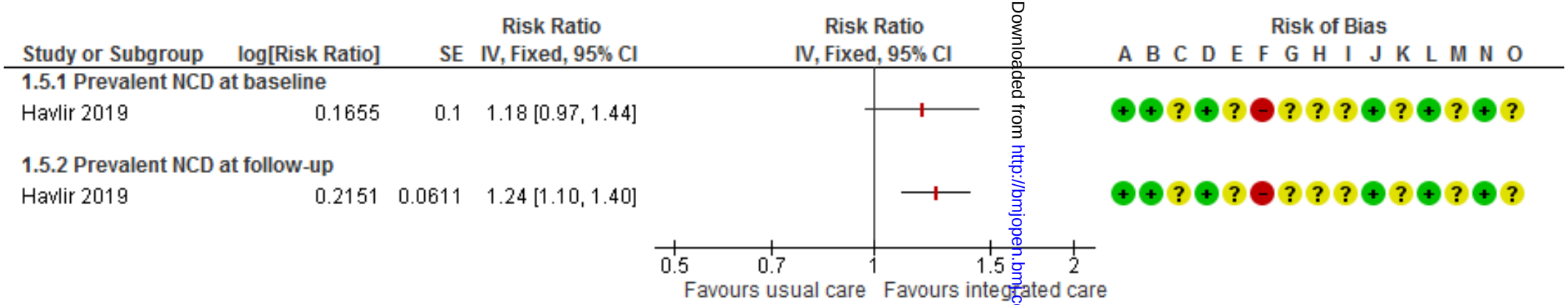
(B) Allocation concealment (selection bias)
(C) Baseline outcome measurements similar
(D) Baseline characteristics similar
(E) Incomplete outcome data (attrition bias)
(F) Blinding of participants and personnel (performance bias)
(G) Blinding of outcome assessment (detection bias)
(H) Protection against contamination
(I) Selective reporting (reporting bias)
(J) Recruitment bias
(K) Baseline differences (clusters)
(L) Loss of clusters
(M) Incorrect analysis
(N) Compatibility with RCTs randomised by individuals
(O) Other bias

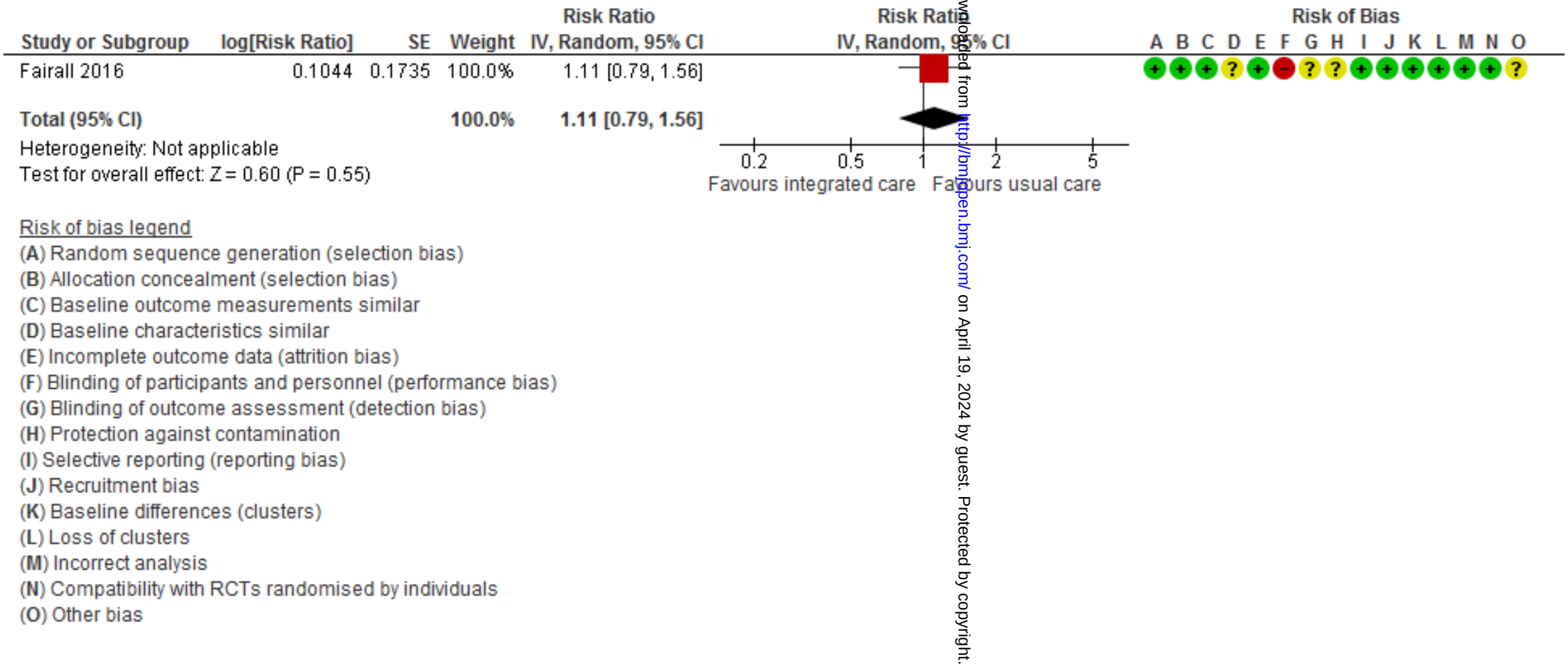
Comparison 1: Integrated models of care vs. usual care
Outcome: NCD and HIV control



Risk of bias legend

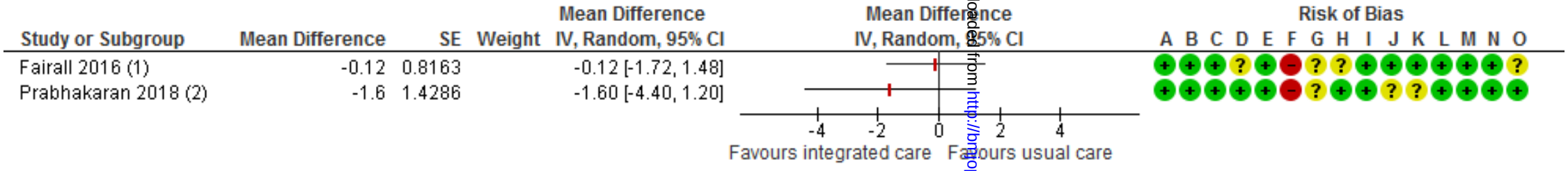
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Baseline outcome measurements similar
(D) Baseline characteristics similar
(E) Incomplete outcome data (attrition bias)
(F) Blinding of participants and personnel (performance bias)
(G) Blinding of outcome assessment (detection bias)
(H) Protection against contamination
(I) Selective reporting (reporting bias)
(J) Recruitment bias
(K) Baseline differences (clusters)
(L) Loss of clusters
(M) Incorrect analysis
(N) Compatibility with RCTs randomised by individuals
(O) Other bias

Comparison 2: Strategies to promote integrated models of care vs. usual care
Outcome: Mortality



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Baseline outcome measurements similar
(D) Baseline characteristics similar
(E) Incomplete outcome data (attrition bias)
(F) Blinding of participants and personnel (performance bias)
(G) Blinding of outcome assessment (detection bias)
(H) Protection against contamination
(I) Selective reporting (reporting bias)
(J) Recruitment bias
(K) Baseline differences (clusters)
(L) Loss of clusters
(M) Incorrect analysis
(N) Compatibility with RCTs randomised by individuals
(O) Other bias

Comparison 2: Strategies to promote integrated models of care vs. usual care
Outcome: Depression



Footnotes

(1) Change from baseline to follow-up; 10-item Center for EpidemiologicStudies...

(2) Value at follow-up; Patient Health Questionnaire-9

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Baseline outcome measurements similar

(D) Baseline characteristics similar

(E) Incomplete outcome data (attrition bias)

(F) Blinding of participants and personnel (performance bias)

(G) Blinding of outcome assessment (detection bias)

(H) Protection against contamination

(I) Selective reporting (reporting bias)

(J) Recruitment bias

(K) Baseline differences (clusters)

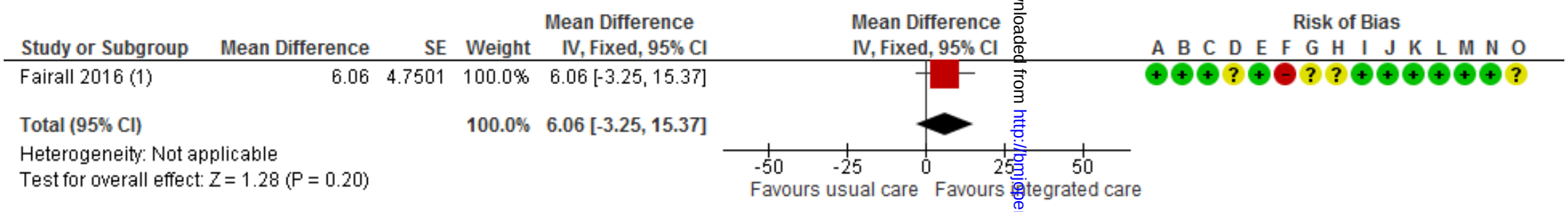
(L) Loss of clusters

(M) Incorrect analysis

(N) Compatibility with RCT of randomised by individuals

(O) Other bias

Comparison 2: Strategies to promote integrated models of care vs. usual care
Outcome: Quality of life



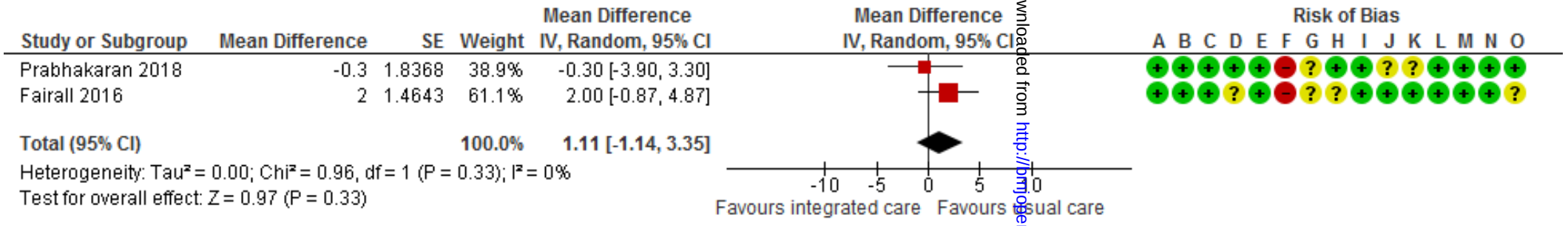
Footnotes

(1) Euro-Qol-5D visual analogue scale: 0=worst imaginable state of health,...

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Baseline outcome measurements similar
(D) Baseline characteristics similar
(E) Incomplete outcome data (attrition bias)
(F) Blinding of participants and personnel (performance bias)
(G) Blinding of outcome assessment (detection bias)
(H) Protection against contamination
(I) Selective reporting (reporting bias)
(J) Recruitment bias
(K) Baseline differences (clusters)
(L) Loss of clusters
(M) Incorrect analysis
(N) Compatibility with RCTs randomised by individuals
(O) Other bias

Comparison 2: Strategies to promote integrated models of care vs. usual care
Outcome: Change in systolic BP



Risk of bias legend
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(B) Allocation concealment (selection bias)
(C) Baseline outcome measurements similar
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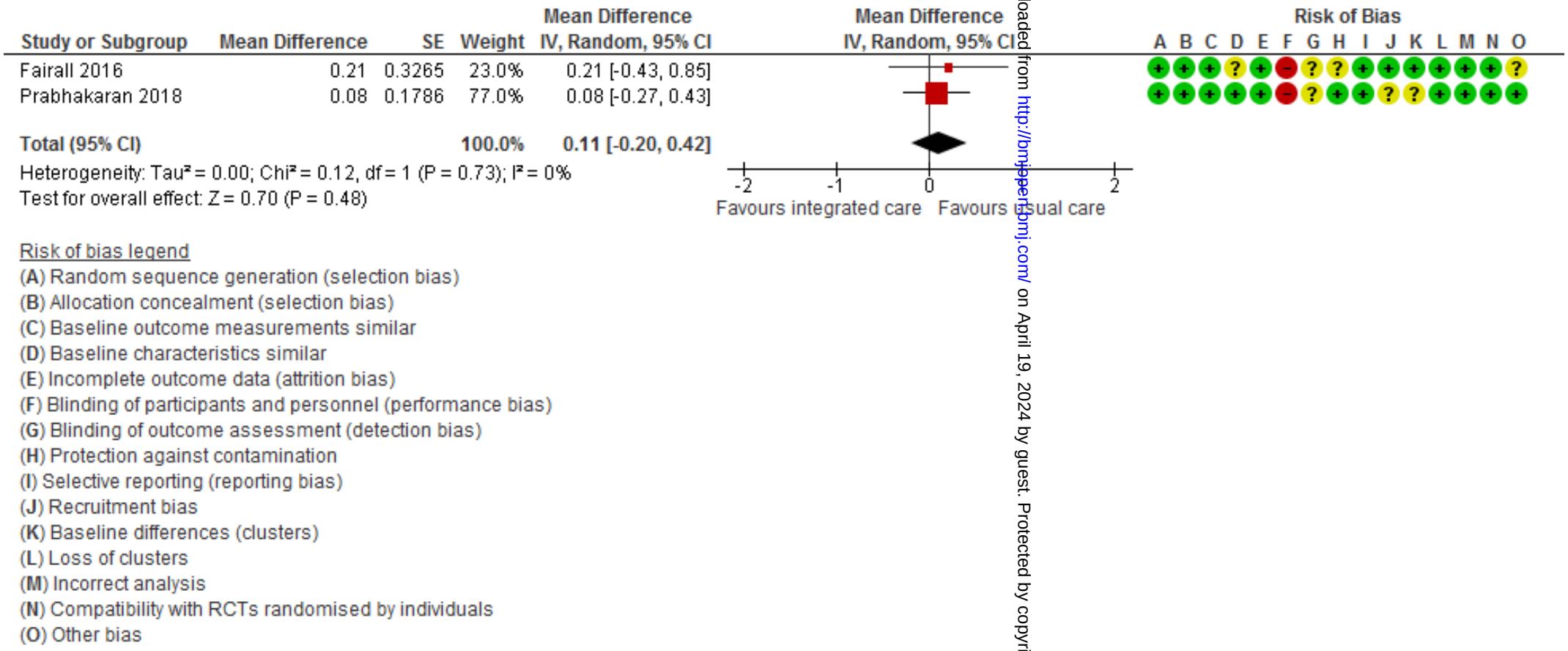
(J) Recruitment bias
(K) Baseline differences (clusters)
(L) Loss of clusters
(M) Incorrect analysis
(N) Compatibility with RCTs randomised by individuals
(O) Other bias

Comparison 2: Strategies to promote integrated models of care vs. usual care
Outcome: Change in HbA1c



Risk of bias legend
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(H) Protection against contamination
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(J) Recruitment bias
(K) Baseline differences (clusters)
(L) Loss of clusters
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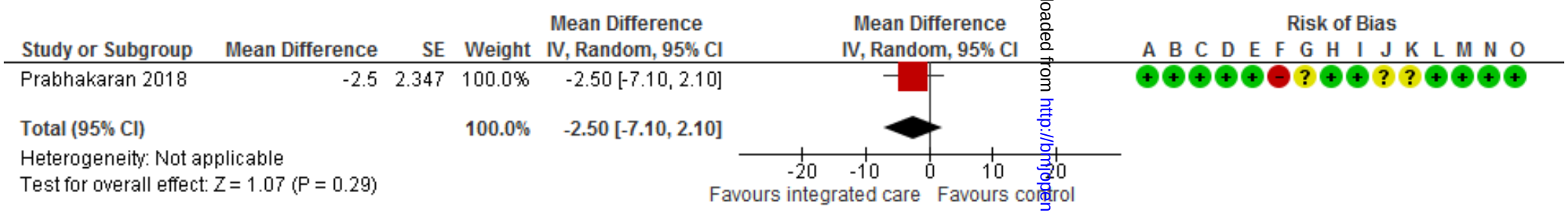
(N) Compatibility with RCTs randomised by individuals
(O) Other bias

Comparison 2: Strategies to promote integrated models of care vs. usual care
Outcome: Change in total cholesterol



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Baseline outcome measurements similar
(D) Baseline characteristics similar
(E) Incomplete outcome data (attrition bias)
(F) Blinding of participants and personnel (performance bias)
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(J) Recruitment bias
(K) Baseline differences (clusters)
(L) Loss of clusters
(M) Incorrect analysis
(N) Compatibility with RCTs randomised by individuals
(O) Other bias

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary file 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6, Figure 2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7-9, Supplementary files 2 and 3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11, Figure 3, 4 and supplementary file 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Supplementary file 5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11-18
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 4 and 5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	19-20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20-21
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	21

PRISMA 2009 Checklist

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

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Effects of integrated models of care for diabetes and hypertension in low-and middle-income countries. A systematic review and meta-analysis

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Effects of integrated models of care for diabetes and hypertension in low- and middle-income countries. A systematic review and meta-analysis

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Word count

6091

Keywords

Integrated care, diabetes, hypertension, low-and middle-income countries

Abstract

Objectives

To assess the effects of integrated models of care for people with multi-morbidity including at least diabetes or hypertension in low-and middle-income countries on health and process outcomes.

Design

Systematic review

Data sources

We searched MEDLINE, EMBASE, CENTRAL, LILACS, Africa-Wide, CINAHL, and Web of Science up to 12 December 2019.

Eligibility criteria

We included randomised controlled trials (RCTs), non-RCTs, controlled before-after studies and interrupted time series (ITS) studies of people with diabetes and/or hypertension plus any other disease, in LMICs; assessing the effects of integrated care.

Data extraction and synthesis

Two authors independently screened retrieved records; extracted data and assessed risk of bias. We conducted meta-analysis where possible and assessed certainty of evidence using GRADE.

Results

Of 7568 records, we included five studies - two ITS studies and three cluster RCTs. Studies were conducted in South Africa (n=3), Uganda/Kenya (n=1), and India (n=1). Integrated models of care compared to usual care may make little or no difference to mortality (very low certainty), the number of people achieving blood pressure (BP) or diabetes control (very low certainty), and access to care (very low certainty); may increase the number of people who achieve both HIV and BP/diabetes control (very low certainty); and may have a very small effect on achieving HIV control (very low certainty). Interventions to promote integrated delivery of care compared to usual care may make little or no difference to mortality (very low certainty), depression (very low certainty) and quality of life (very low certainty); and may have little or no effect on HbA1c (low certainty), systolic BP (low certainty), and total cholesterol levels (low certainty).

Conclusions

Current evidence on the effects of integrated care on health outcomes is very uncertain. Programmes and policies on integrated care must consider context-specific factors related to health systems and populations.

PROSPERO registration: CRD42018099314

Strengths and limitations of this study

- We included study designs that are able to provide reliable evidence on the effects of integrated models of care on health and process outcomes
- We performed a comprehensive search for published and unpublished studies up to 12 December 2019, with no language restrictions.

- We assessed the certainty of evidence using the GRADE approach taking into consideration study limitations, inconsistency, imprecision, publication bias and indirectness when downgrading the certainty of evidence.
- Our review did not aim to answer questions on aspects linked to implementation of integrated models of care and barriers and facilitators to integrated models of care at individual and health-system level

Introduction

Low- and middle-income countries (LMICs) are facing an increasing burden of non-communicable diseases (NCDs).[1] A recent report of the World Health Organization (WHO) on NCDs indicates that 41 million people succumb to NCDs globally which is the equivalent of 71% of total global deaths. Fifteen million people die prematurely due NCDs every year (between the ages of 30 and 69 years) and 85% of these premature deaths occur in LMICs.[1 2] Furthermore, NCDs are projected to exceed communicable, maternal, perinatal, and nutritional diseases as the most common causes of death by 2030.[3] In LMICs, the vast majority of NCD deaths are caused by cardiovascular diseases (CVDs), mainly due to coronary artery diseases and stroke,[4] diabetes, cancer and chronic respiratory diseases; and they account for 54% of NCD disability adjusted life years.[1 5] Diabetes and hypertension are the major cardiovascular risk factors for target organ damage of brain, heart and kidney.[1]

Currently, it is estimated that 425 million people in LMICs live with diabetes. This number is expected to increase up to 629 million in 2045.[6] According to the International Society of hypertension, around 40% of people over age of 25 years have hypertension worldwide and two thirds of them live in LMICs.[7] Due to the existing high burden of communicable diseases, especially HIV infection, in sub-Saharan Africa and other LMICs, a lot of people are living with multi-morbidity. Because of the progress made with scaling up of anti-retroviral therapy (ART), the life expectancy of people living with HIV (PLHIV) has increased substantially, putting them at risk of NCDs that are common in older people. In addition to the traditional risk factors for NCDs, such as smoking, poor diet and a sedentary lifestyle, PLHIV have an increased risk of NCDs (especially CVD, cervical cancer, depression and diabetes), related to HIV itself and to ART related side effects[8-11] According to a recent systematic review examining the prevalence of NCDs among PLHIV in LMICs,[12] the pooled prevalence estimate of hypertension was 21.2% (95%CI 16.3 to 27.1); while that of depression was 24.4% (95%CI 12.5 to 42.1%). The prevalence of diabetes among PLHIV was reported to be between 1.2 and 18% and authors ascribed the variation in the findings to actual differences in populations, as well as the lack of standardised diagnostic criteria for diabetes.

In LMICs, people with NCDs such as diabetes and hypertension are generally characterised by very poor outcomes due to various other factors such as limited access to reliable healthcare services.[13] The chronic nature of NCDs puts strain on the already scarce resources of healthcare systems and affected individuals in LMICs.[14] Hence there is a need to design effective interventions to address the increasing burden of NCDs such diabetes and hypertension, in particular in complex patients with co-morbidities such as HIV infection and other CVDs. Provision of integrated care has been advocated by researchers and many international bodies such as the WHO as a way of tackling the rising burden of NCDs and strengthening the health systems particularly in LMICs.[15-17] Recent studies from LMICs have assessed integration of HIV/AIDS and tuberculosis (TB) services at primary healthcare (PHC) level, [18-20] which is usually the first point of contact with health services for people living in LMICs. Based on these integrated models of care, we conceptualised integrated care either as partial integration or full integration as illustrated in Figure 1.[21] Fully integrated care is seen as a “one-stop-shop” model whereby a patient receives all necessary care or services under one roof by one or more health-care professionals. In a partially integrated model of care, patients receiving treatment for one disease

such as diabetes receive additional care related to either prevention, diagnosis or treatment of another disease, but do not receive the full package of care [21].

Although integrated models of care have been widely advocated, and various models and programmes have been implemented and described, there is a lack of evidence on the effectiveness of integrated care compared to other models of care in LMICs. We previously conducted a scoping review to assess existing systematic reviews on the effectiveness of integrated models of care in people with diabetes or hypertension and any other comorbid disease. [22] We found five reviews[23-27] that met our inclusion criteria, but only one of these included studies conducted in LMICs. Furthermore, none of the included studies assessed integrated care for diabetes or hypertension and communicable diseases (e.g. HIV). A subsequent systematic review by Haldane and colleagues examined existing programmes of integrated healthcare delivery for diabetes, hypertension or CVDs with HIV/AIDS.[28] However, included studies mostly described existing programmes with no thorough evaluation of the effectiveness of these programmes. A descriptive study from Cambodia looked at the management of HIV/AIDS, diabetes, and hypertension and found that integration of services for these conditions was highly acceptable and led to good health outcomes with improved CD4 count, glycated haemoglobin (HbA1c) and blood pressure levels.[29] Dudley and Garner[30] assessed the effectiveness of strategies to integrate PHC services in LMICs. They included studies that integrated family planning into existing services; nutrition and infectious disease interventions; and sexually transmitted infections (STIs), HIV/AIDS and TB treatment. None of the included studies reported on NCDs.

In light of limited information in existing reviews, we conducted this review to assess the effects of integrated models of care at PHC level for people living in LMICs, with multi-morbidity, of which diabetes or hypertension is one, compared to no integrated care on health and process outcomes.

Methods

Our systematic review followed the methods pre-specified in a published protocol.[21] We followed the PRISMA reporting guideline to report on the findings of our systematic review.

Criteria for considering studies for inclusion

Types of study designs

Randomised controlled trials (RCTs), including cluster RCTs, controlled (non-randomised) clinical trials (CCTs) or cluster non-randomised trials, interrupted time series (ITS) studies with at least three data points before and after the intervention, and controlled before-and-after (CBA) studies were eligible for inclusion. Cluster randomised, cluster non-randomised or CBA studies were only included if there were at least two intervention sites and two control sites.

Types of participants

We included studies with adults and children attending PHC clinics, presenting with diabetes or hypertension plus one or more other chronic diseases (multi-morbidity), or risk factors for other chronic diseases in LMICs. We defined LMICs according to the 2016 classification of the World Bank,[31] that defined low-income economies as those with a gross national income (GNI) per capita of $1035 or less, lower middle income economies as those with a GNI per capita of $1006 to $3995, and upper middle economies as those with a GNI per capita of $3956 to $12235.

Types of interventions

Eligible interventions were models of full or partial integration of services at PHC and community level. Full integration of service delivery was defined as models where patients (primarily treated for

diabetes, hypertension or any other disease) received the full package of care (prevention, diagnosis and treatment) for diabetes or hypertension and any other chronic disease at the same point of care by one or more healthcare professionals. Partial integration of services was defined as models where patients treated for diabetes, hypertension, or any other chronic disease received part of the package of care (either prevention, diagnosis, or treatment) for another disease (see Figure 1). Partially integrated models of care therefore refer to a lower level of integration compared to fully integrated models of care. For example, with partially integrated care, patients receiving treatment for hypertension would be tested for HIV and referred for treatment; whereas with fully integrated care, patients receiving treatment for hypertension would be tested and treated for HIV during the same clinic visit.

Included studies did not provide adequate information for us to categorise interventions as fully integrated models of care or partially integrated models of care and we thus categorised interventions as integrated models of care and interventions that promoted integrated delivery of care. Integrated models of care assessed the effect of integration of service delivery i.e. integration of two previously separate models of delivery of care into one model of delivery of care, for example integrating HIV services into general PHC services. We distinguished these interventions from interventions that promoted an integrated approach to providing care in PHC facilities. In these cases, services as such were not integrated, but healthcare workers were encouraged to provide holistic patient care, for example through the provision and use of clinical management tools that supported an integrated approach to care.

Types of comparisons

We aimed to compare fully integrated models of care to stand-alone care; partially integrated models of care to stand-alone care; and fully integrated models of care to partially integrated models of care. However, for all included studies, comparisons were reported as standard or usual care and authors did not provide an adequate description of what that entailed. Although these seemed to refer to less integrated care, we unable to categorise them as partially integrated models of care or stand-alone care. We therefore compared integrated models of care to usual care, and interventions to promote integrated delivery of care to usual care.

Types of outcomes

We included studies that reported on either primary or secondary outcomes, as defined by primary study authors. Primary outcomes were all-cause mortality, disease specific morbidity as reported in included studies (e.g. disease control metrics), quality of life, glycated haemoglobin (HbA1c), systolic Blood pressure (SBP) and cholesterol levels. Secondary outcomes were access to care, retention in care, adherence, continuity of care, quality of care and cost of care.

Search strategy

We searched MEDLINE (PubMed), EMBASE (Ovid), the Cochrane Central Register of Controlled Trials (CENTRAL), LILACS, Africa-Wide Information (via EBSCO host), CINAHL, and Web of Science (Core collection) (Date of last search: 12 December 2019). We searched the WHO International Clinical Trials Registry Platform (ICTRP) and Clinicaltrials.gov for ongoing studies, as well as conference abstracts from the International AIDS Society Online Resource Library, the HIV/AIDS Implementers' Meetings and the NCDs Alliance meetings. Search terms included 'diabetes', 'hypertension', 'comorbidities', 'integrated health care delivery', 'low-and middle-income countries', and their synonyms. The full search strategies for all databases are provided in Supplementary file 1. To supplement the search of electronic databases, we screened reference lists of included studies and reference lists of relevant systematic reviews, and contacted experts in the field and relevant organisations (e.g. NCD Alliance) for unpublished studies. We did not have any restrictions related to language, date of publication or publication status.

Selection of studies

Two authors (JUN and AR or a research assistant) independently screened titles and abstracts of studies identified by the search, using Covidence software.[32] We retrieved full texts of potentially eligible studies. Two authors (JUN and AR/TY/CMB) independently screened full texts for eligibility. Discrepancies were resolved through discussion with a third author (JJM/IT). We classified studies as included, excluded or ongoing and provided reasons for excluding studies.

Data extraction

Two authors (JUN, AR and IT) independently extracted data for included studies using a pre-specified, piloted data extraction form and assessed risk of bias. Discrepancies were resolved through discussion or by consulting a third author (TY/JJM). We extracted data related to the study design, participants, intervention, comparison, outcomes, setting, context and funding sources. We used the template for intervention description and replication (TIDieR)[33] and the PRISMA-Complex Interventions extension checklist[34] to guide data extraction and reporting related to the interventions.

Risk of bias assessment

We used guidance from Cochrane Effective Practice and Organisation of Care (EPOC) to assess risk of bias for included studies[35]. Risk of bias was assessed as low, high, or unclear for each domain. For RCTs, non-randomised trials and CBA studies, we assessed the following nine domains: 1) random sequence generation, 2) allocation concealment, 3) baseline outcome measurements, 4) baseline characteristics, 5) incomplete outcome data, 6) knowledge of allocated intervention (blinding), 7) protection against contamination, 8) selective outcome reporting and 9) other risks of bias. For cluster RCTs, we assessed additional risk of bias linked to recruitment, cluster baseline differences, loss of clusters, incorrect analysis and compatibility with RCTs randomised by individuals, as per the Cochrane handbook.[36] For ITS studies, we assessed whether 1) the intervention was independent of other changes, 2) the shape of the intervention effect was pre-specified, 3) the intervention was unlikely to affect data collections, 4) knowledge of the allocated intervention was adequately prevented during the study, 5) incomplete outcome data was likely to bias results, 6) outcomes were reported selectively and 7) there were any other risks of bias.

Data analysis

We extracted relevant data for each outcome per included study. For dichotomous outcomes, we reported risk ratios (RR) and 95% confidence intervals (CI). For continuous outcomes, we reported mean differences (MD) with 95% CI if outcomes were measured in the same way across studies, or standardised mean differences (SMD) with 95% CI where outcomes were measured differently across studies and where standard deviations (SD) were reported. For ITS studies, we reported beta coefficients (β) with 95% CI or standard error (SE). We contacted study authors to request information on missing data. We did not impute any data.

All included cluster RCTs appropriately adjusted for the effects of clustering in their analysis, we thus used these adjusted effect estimates and standard errors in our meta-analysis using the generic inverse-variance method in Review Manager 5.[37] We did not include studies with more than one treatment arm in our review.

We explored clinical heterogeneity by clearly documenting study characteristics related to the population, intervention, outcomes and context in table format. We assessed statistical heterogeneity in each meta-analysis by inspecting forest plots and calculating Chi^2 test values and I^2 statistics. We considered heterogeneity to be important if the p-value of the Chi^2 test was < 0.10, and the I^2 statistic was above 30%, as per the recommendations in the Cochrane handbook.[36]

We pooled data from individual studies if we judged them to be sufficiently homogeneous in terms of design, population, intervention and comparator. As we anticipated some degree of heterogeneity, we performed random-effects meta-analysis. We did not pool data from RCTs and non-randomised studies in a single meta-analysis. Where we judged included studies to be too heterogeneous to pool, we used narrative synthesis and presented data in tabular format. We did not perform subgroup or sensitivity analysis, as only two studies contributed to the meta-analysis. We were unable to examine reporting biases by means of funnel plots, as we only included two studies in the meta-analysis.

Certainty of evidence

We assessed the certainty of the evidence using GRADE[38] for the following outcomes: mortality, disease specific morbidity, quality of life, HbA1c, systolic BP, cholesterol levels and access to care. We created a 'Summary of findings' table using GRADEpro software.[39] Our judgements to downgrade the certainty of evidence were based on assessment of the following five domains: 1) study limitations, 2) inconsistency, 3) imprecision, 4) indirectness and 5) publication bias. According to GRADE guidance, non-randomised studies (such as CBAs and ITS studies) start at low certainty evidence. We considered upgrading the certainty of evidence for non-randomised studies if there was a large effect, a dose-response and cases where all plausible residual confounding would reduce a demonstrated effect or would suggest a spurious effect if no effect was observed.

For each outcome, we described the certainty of evidence as high, moderate, low or very low.[40] For outcomes reported by both RCTs and non-randomised studies, we made separate GRADE judgements for both types of studies. Where we arrived at the same level of certainty of evidence, we summarised this in a single judgement per outcome. We interpreted the certainty of evidence according to guidance provided by the GRADE working group, which takes into consideration the size of the effect and the certainty of evidence.[41]

Patient and public involvement

No patients were involved in the development of this systematic review.

Results

The results of the search are depicted in the PRISMA flow diagram (Figure 2). We screened titles and abstracts of 7568 records. We obtained and screened full texts of 49 potentially relevant studies. We included five studies,[42-46] (Table 1) reported in six articles and excluded 37 articles and reported reasons for exclusion (Supplementary file 2). For one study[47] that met eligibility criteria, we were only able to access the conference abstract. We classified this study as 'awaiting assessment', as we are unable to definitively decide on inclusion or exclusion until we have access to the full report. We identified five ongoing RCTs,[48-51] investigating integrated care for depression and hypertension in China;[48] integrated care for depression and hypertension[49] or depression and diabetes/HIV[50] in South Africa; integrated care for common mental disorders and hypertension, diabetes or ischemic heart disease in India;[51] and diabetes and TB in India.[52]

Table 1: Summary of characteristics of included studies

Study ID	Study design	Country and Setting	Participants	Intervention	Control	Study duration (follow-up)	Outcomes[1]
Integrated models of care							
Ameh 2017[42]	Controlled ITS study	South Africa: Primary health care (PHC) facilities, Ehlanzeni health district, Mpumalanga Province	Patients with chronic disease (HIV, diabetes or hypertension) n=878	Integrated chronic disease management (ICDM) model Clinics: n=7 Participants: n=435 (Hypertension: n=210; Diabetes: n=2; HIV: n=141; Comorbidities: n=82)	Usual care in PHC facilities Clinics: n=5 Participants: n=443 (Hypertension: n=91; Diabetes: n=2; HIV: n=282; Comorbidities: n=68)	30 months Pre-intervention: 6 months Post-intervention: 24 months	- **Blood pressure (BP) control[2]** - **CD4 count control[3]** - **Number of healthcare visits**
Havlir 2019[46]	Cluster RCT	Kenya and Uganda: Rural regions in south-western and eastern Uganda, and western Kenya	Clusters: Communities of 9000 to 11 000 people Participants: People residing in community n=150 395 (baseline)	Integrated care: Baseline HIV and multi-disease testing plus annual testing, universal ART and streamlined, patient-centered care Clusters: n=16 Participants: n=79 818 (baseline) (Hypertension in adults over 30 years: n=5953)	Usual care: Baseline HIV and multi-disease testing and national guideline-restricted ART, hypertension and diabetes care as per country standard of care (not integrated) Clusters: n=16 Participants: n=70 577 (baseline)	36 months	- Cumulative HIV incidence - Time to initiation of ART - Viral suppression - **Death** - Incident tuberculosis or death due to illness - **Control of hypertension[4] among HIV-infected persons** - **Control of diabetes[5] or hypertension (NCD) among HIV infected persons** - **Control of HIV[6] and hypertension** - **Control of HIV and NCDs[7]**

[1] Outcomes relevant to this review are in bold
[2] Defined as: BP <140/90mmHg
[3] Defined as: CD4 count >350 cells/mm^3
[4] Defined as: At least one systolic BP measurement <140mmHg, and at least one diastolic measurement of <90mmHg
[5] Defined as: Finger prick blood glucose ≤11 mmol/L
[6] Defined as: Suppressed viral replication (<500 copies/ml)
[7] Defined as: Control of all prevalent NCDs (hypertension or diabetes)

					(Hypertension in adults over 30 years: n=5911)		- Control of hypertension in the overall population - Control of diabetes in the overall population
Rawat 2018[45]	ITS study	South Africa: PHC clinics in the Free state Province	Patients attending PHC clinics (focus on diabetes and hypertension) n=not reported	Integration of HIV care into HC facilities n=131 clinics	No control group	48 months Pre-intervention: 12 months Post-intervention: 36 months	- **Population level new diabetics on treatment** - **Clinic level new diabetics on treatment** - **Population-level new hypertensive on treatment** - **Clinic level new hypertensive on treatment** - **Total ART patients** - **New patients initiated on ART**
Interventions to promote integrated delivery of care							
Fairall 2016[43]	Cluster RCT	South Africa: Mostly rural PHC clinics in Eden and Overberg districts, Western Cape Province	Patients with one or more of the following: hypertension, diabetes, chronic respiratory disease, depression n=4393	Primary Care (PC) 101 management tool Clinics: n=19 Participants: n=2166 (Hypertension: n=1555; diabetes: n=851)	Usual care: Practical Approach to Lung Health and HIV/AIDS in South Africa (PALSA PLUS) management tool Clinics: n=19 Participants: n=2227 (Hypertension: n=1672; diabetes: n=991)	14 months	- Treatment intensification for hypertension, diabetes and chronic respiratory disease - **Depression** - CVD risk - **Systolic BP** - **HbA1C** - Body Mass Index (BMI) - Smoking status - **Health-related quality of life** - **Mortality** - **Healthcare utilisation**
Prabhakaran 2019[44]	Cluster RCT	India: Community Health Centres (CHC) from 4 districts in Haryana and 2 districts in Karnataka	Patients with confirmed diagnosis of diabetes or hypertension n=3698	mWellcare system CHCs: n=20 Participants: n=1842	Enhanced usual care CHCs: n=20 Participants: n=1856	12 months	- **Mean change in systolic BP** - **Mean change in HbA1C** - Mean change in fasting plasma glucose - **Mean change in total cholesterol** - Mean change in CVD risk - Mean change in Tobacco use - Mean change in BMI - Alcohol use

							- **Depression score** - **Adherence** - **Perceived quality of care**

Characteristics of included studies

We included three cluster RCTs and two ITS studies. One cluster RCT was conducted in South Africa,[43] one in India,[44] and the Sustainable East Africa Research in Community Health (SEARCH) trial was conducted in Uganda and Kenya.[46] The two ITS studies were both conducted in South Africa[42 45] (Table 1). All studies were conducted in PHC facilities in mostly rural settings. All five studies assessed the effect of strategies for full integration of care compared to partial integration of care.

The two ITS studies[42 45] and the SEARCH trial[46] assessed the effects of integrated models of care for chronic diseases (Table 2). Ameh and colleagues[42] conducted a controlled ITS study, comparing the integrated chronic disease management (ICDM) model to usual care over a period of 30 months. Rawat and colleagues[45] examined the effect of integrating HIV care into PHC clinics over a 48 months period. The SEARCH trial[46] assessed the effects of universal ART and streamlined, patient-centered care (integrated care) compared to usual care as per national guidelines. Interventions are described in more detail according to the TIDieR checklist in supplementary file 3.

The other two cluster RCTs[43 44] assessed the effectiveness of interventions to promote integration of care (Table 2). Fairall and colleagues[43] introduced the Primary Care (PC) 101 clinical management tool to promote provision of comprehensive care for all symptoms including NCDs, HIV, TB, mental health and women's health, in PHC clinics randomised to the intervention, while the control clinics continued using the Practical Approach to Lung Health and HIV/AIDS in South Africa (PALSA PLUS) management tool, which did not cover all NCDs and was the standard of care at the time of the trial. Prabhakaran and colleagues[44] introduced the mWellcare system, a m-health based electronic decision support system, to promote integrated management of hypertension, diabetes, depression, and alcohol and tobacco use in PHC centres randomised to the intervention. Control centres continued with usual care. Interventions are described in more detail according to the TIDieR checklist in supplementary file 4.

Table 2: Key components of included interventions

Name and Study ID	**Components related to provision of care in the clinic**	**Components related to provision of care in the community/at home**	**Training**	**Appointment reminders**
Integrated chronic disease management (ICDM) model Ameh 2017	Facility reorganisation: designated chronic care area; supply of critical medicines; pre-packaging of medication Clinical management support: use of guidelines to manage chronic diseases (PC101); human resources audit; capacity building; appropriate referral	Ward-based outreach teams to ensure individual responsibility and "assisted" self-management Health promotion and population screening	-	-

National policy to integrate HIV care into all PHC facilities Rawat 2018	Policy to integrate HIV care into PHC clinics Either disease-specific nurses in separate consulting rooms (co-location), or one nurse that provided comprehensive care for all diseases in single consultation room Additional staff to strengthen drug delivery systems	-	Training of nurses in comprehensive management of HIV: Nurse initiated Management of ART (NIMART) Training of nurses through the Practical Approach to Lung Health in South Africa (PALSA PLUS)	-
SEARCH intervention Havlir 2019	Patient-centered, integrated care for HIV, diabetes, hypertension: 3-month visit intervals; ART to all HIV positive participants; hypertension and diabetes treated according to standard algorithms	Community health campaigns (CHCs): Testing for HIV, diabetes and hypertension; counselling and clinic appointments; blood tests for HIV positive participants; transportation voucher for first clinic visit Home-based testing for participants that did not attend CHCs Appointments to initiate ART within 7 days for HIV positive participants not on ART; introductory phone call from clinic staff; support hotline available via phone or text message	-	Phone/SMS reminders about clinic visits
Primary Care (PC) 101 Fairall 2016	PC 101 guideline: Ring-bound, colour illustrated booklet Expanded prescribing provisions for nurses Desk pads with key messages	-	Training of facility trainers Educational outreach sessions by facility trainers	Letters and SMS reminders of follow-up visits

mWellcare Prabhakaran 2018	mWellcare system: m-Health-based electronic decision-support system Visible charts on the management of the conditions Onsite supervision and support	Pamphlets containing lifestyle advice	Training of physicians on current clinical management guidelines and orientation to mWellcare Training of nurses in management of hypertension, diabetes, depression, and tobacco and alcohol use	SMS reminders of follow-up visits and medication adherence

Risk of bias in included studies

For the two ITS studies, we judged risk of bias to be low or unclear in all domains (Figure 3). For the three cluster RCTs, we judged risk of selection bias to be low, risk of performance bias to be high, as blinding of participants and personnel was not possible due to the nature of the interventions, and risk of detection bias to be unclear for all three studies. We judged attrition bias to be low for two cluster RCTs[43 44] and unclear for the SEARCH trial[46] (Figure 4). Detailed judgements for each included study are reported in supplementary file 5.

Integrated models of care compared to usual care

We included three studies as part of this comparison.[42 45 46] Results are summarised in the summary of findings table (Table 3) and forest plots are available in supplementary file 6.

Table 3: Summary of findings for integrated models of care compared to usual care for diabetes and hypertension in LMICs

Patient or population: Patients with multi-morbidity (diabetes and/or hypertension and other chronic conditions e.g. HIV)
Setting: Low- and middle-income countries
Intervention: Integrated care for hypertension, diabetes and HIV
Comparison: Usual care

Outcome	Effect (95%CI)	No of participants (studies)	Certainty of evidence (GRADE)	Comments
Mortality	RR 0.90 (0.79 to 1.02) Risk with usual care: 0.56 per 100 person-years Risk with integrated care: 0.51 per 100 person-years	171 431 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	Integrated care compared to usual care may make little or no difference to the rate of death, but the evidence is very uncertain
BP control (number of PLHIV achieving BP control)	RCT: Prevalent hypertension at baseline: RR 1.09 (0.98 to 1.21) RCT: Prevalent hypertension at follow-up: RR 1.16 (0.99 to 1.36) ITS study: β=0.010 (0.003 to 0.016)	2319 (2 studies: 1 RCT, 1 ITS study)	⨁◯◯◯ VERY LOW [a,c,d,e,f]	Integrated care compared to usual care may make little or no difference to achieving BP control but the evidence is very uncertain
BP or diabetes (NCD) control (number of PLHIV achieving NCD control)	Prevalent NCD at baseline: RR 1.06 (0.88 to 1.27) Prevalent NCD at follow-up: RR 1.13 (0.97 to 1.32)	1 RCT*	⨁◯◯◯ VERY LOW [a,c,d]	Integrated care compared to usual care may make little or no difference to achieving NCD control but the evidence is very uncertain
HIV control (CD4 count control)	β=0.057 (0.056 to 0.058)	878 (1 ITS study)	⨁◯◯◯ VERY LOW [e,f]	Integrated care may have a very small effect on achieving CD4 count control, but the evidence is very uncertain
BP and HIV control (number of people achieving both HIV viral suppression and BP control)	Prevalent hypertension at baseline: RR 1.22 (1.08 to 1.37) Prevalent hypertension at follow-up: RR 1.24 (1.10 to 1.40)	1441 (1 RCT)	⨁◯◯◯ VERY LOW [a,c,d]	Integrated care compared to usual care may result in a slight increase in the number of people achieving both BP and HIV control but the evidence is very uncertain
BP or diabetes (NCD) and HIV control (number of people achieving both HIV viral suppression and NCD control)	Prevalent NCD at baseline: RR 1.18 (0.97 to 1.44) Prevalent NCD at follow-up: RR 1.24 (1.10 to 1.40)	1441 (1 RCT)	⨁◯◯◯ VERY LOW [a,c,d]	Integrated care compared to usual care may result in a slight increase in the number of people achieving both NCD and HIV control but the evidence is very uncertain
Quality of life	-	-	-	Not reported
Systolic BP	-	-	-	Not reported
HbA1c	-	-	-	Not reported
Cholesterol levels		-	-	Not reported

Access to care	There was no change in trend from pre- to post-intervention for population level new diabetics on treatment, clinic level new diabetics on treatment and clinic-level new hypertensive patients on treatment. There was a slight decrease in new hypertensive patients on treatment at population level at 36 months	1 ITS*	⊕◯◯◯ VERY LOW e,g	Integrated care may make little or no difference to short term access to care and may result in a slight decrease in long-term access to hypertensive care, but the evidence is very uncertain.

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; BP: Blood pressure; HIV: Human Immunodeficiency Virus; HbA1c: Glycated Haemoglobin; NCD: Non-communicable disease; RCT: Randomised controlled Trial; ITS: Interrupted time series

*Sample size not reported

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Footnotes: Explanation of GRADE certainty of evidence

Randomised controlled trials:

a) Downgraded by 1 due to study limitations: high risk of performance bias and unclear risk of bias for other domains

b) Downgraded by 1 due to indirectness: Results are based on number of participants at baseline, however authors did not report how many participants had HIV plus hypertension/diabetes at baseline. At 3-year follow-up, less than 1% of participants at follow-up had hypertension/diabetes and HIV infection (0.7% (694/103 777) in the control group and 0.6% (747/121 347) in the intervention group)

c) Downgraded by 1 due to indirectness: Usual care comprised care according to national guidelines in Kenya and Uganda. Authors did not report what this entails. It is not clear to what extend care was integrated or not

d) Downgraded by 1 due to imprecision: Small sub-sample with hypertension and HIV in the RCT with wide 95% confidence intervals

Interrupted time series studies:

e) Observational study, starting at low certainty evidence

f) Downgraded by 1 due to indirectness: Intervention clinics experienced stock-outs of anti-hypertensive drugs and malfunctioning of BP machines. We are therefore not confident that the intervention was delivered as intended

g) Downgraded by 1 due to indirectness: Study reported on population level new diabetics on treatment, clinic level new diabetics on treatment, population level new hypertensive patients on treatment and clinic level new hypertensive patients on treatment. This is an indirect measure of access to care

All-cause mortality: The SEARCH trial[46] reported the rate of all-cause mortality among baseline residents in included communities. Results suggest that integrated compared to usual care may make little or no difference to the mortality rate when compared to usual care but the evidence is very uncertain (RR 0.90 95%CI 0.79 to 1.02, n=171 431, 1 RCT, very low-certainty evidence).

Disease-specific morbidity (BP control): Integrated care compared to usual care may make little or no difference to achieving BP control, but the evidence is very uncertain. Results from the SEARCH trial[46] suggest that integrated care compared to usual care may make little or no difference to the number of PLHIV who achieve BP control with prevalent hypertension at baseline (RR 1.09, 95%CI 0.98 to 1.21, 1 RCT, very low-certainty evidence) and PLHIV with prevalent hypertension at follow-up (RR 1.16, 95%CI 0.99 to 1.36, n=1441, 1 RCT, very low- certainty evidence). Results of the controlled ITS study[42] suggest that integrated care compared to usual care may increase the probability of

achieving BP control by 1%, but the evidence is very uncertain (β=0.010, 95%CI 0.003 to 0.016, n=878, 1 ITS study, very low-certainty evidence).

Disease-specific morbidity (NCD control): Results from the SEARCH trial [46] suggest that integrated care compared to usual care may make little or no difference to the number of PHLV who achieve NCD (diabetes and/or hypertension) control with prevalent NCD at baseline (RR 1.06, 95%CI 0.88 to 1.27, 1 RCT, very low-certainty evidence) and prevalent NCD at follow-up but the evidence is very uncertain (RR 1.13, 95%CI 0.97 to 1.32, 1 RCT, very low-certainty evidence).

Disease-specific morbidity (HIV control): One ITS study[42] reported on HIV control in terms of CD4 count control. Results suggest that integrated care compared to usual care may increase the probability of achieving CD4 count control by 6%, but the evidence is very uncertain (β=0.057, 95%CI 0.056 to 0.058, n=878, 1 ITS study, very low-certainty evidence).

Disease-specific morbidity (HIV and BP control): Results from the SEARCH trial[46] suggest that integrated care compared to usual care may increase the number of PLHIV who achieve both HIV viral suppression (HIV control) and BP control with prevalent hypertension at baseline (RR 1.22, 95%CI 1.08 to 1.37, 1 RCT, very low-certainty evidence) and with prevalent hypertension at follow-up (RR 1.24, 95%CI 1.10 to 1.40, n=1441, 1 RCT, very low-certainty evidence).

Disease-specific morbidity (HIV and NCD control): Integrated care compared to usual care may make little or no difference to the number of PLHIV who achieve both HIV viral suppression (HIV control) and NCD control with prevalent NCD at baseline (RR 1.18, 95%CI 0.97 to 1.44, 1 RCT, very low certainty), but may result in a slight increase in the number of PLHIV who achieve both HIV viral suppression (HIV control) and NCD control with prevalent NCD at follow-up (RR 1.24, 95%CI 1.10 to 1.40, 1 RCT very low-certainty evidence). However, the evidence is very uncertain for these outcomes.

Access to care: One ITS study reported on access to care[45] in terms of the change in post-integration trend compared to pre-integration trend for population level new diabetics on treatment, clinic level new diabetics on treatment, population-level new hypertensive patients on treatment, and clinic level new hypertensive patients on treatment. Integrated care may make little or no difference to population level new diabetics on treatment at 18 (1/100 000, Standard Error (SE)=2, p=0.50, very low certainty) and 36 months (1/100 000, SE=3, p=0.61, very low-certainty evidence) post-integration; clinic level new diabetics on treatment at 18 (0/100 000, SE=1; p=0.96, very low-certainty evidence) and 36 months post-integration; clinic level new hypertensive patients on treatment at 18 (0/100 000, SE=1; p=0.78, very low-certainty evidence) and 36 months (0/100 000, SE=0; p-value=0.57, very low-certainty evidence) post-integration, and population level new hypertensive patients on treatment at 18 months post-integration (-7/100 000, SE=4; p=0.08, very low-certainty evidence). Results suggest that there was a slight decrease in population level new hypertensive patients on treatment at 36 months post-integration (-6/100 000; SE=3; p=0.02, very low-certainty evidence). However, the evidence is very uncertain for these outcomes.

Authors also reported on the total number of patients on anti-retroviral treatment (ART) and the number of new patients initiated on ART. Overall, the number of patients for both outcomes increased during each year of follow-up. No effect size was reported. No other secondary outcomes were reported for this comparison.

Interventions to promote integrated delivery of care compared to usual care

We included two studies in this comparison.[43 44] Results are summarised in the summary of findings table (Table 4) and forest plots are available in supplementary file 6.

All-cause mortality: Results from one cluster RCT[43] suggest that interventions to promote integrated care compared to usual care may make little or no difference in mortality (RR 1.11; 95% CI 0.79 to 1.56; n=3393; 1 RCT, very low-certainty evidence) when compared to usual care, but the evidence is very uncertain.

Disease-specific morbidity (depression): Results from two RCTs[43 44] suggest that interventions to promote integrated care compared to usual care may make little or no difference to depression scores, but the evidence is very uncertain. Fairall 2016 reported the change in depression scores from baseline to follow up using the 10-item Center for Epidemiologic Studies Depression Scale and reported no difference between groups (MD −0.12; 95%CI −1.72 to 1.48; n=3976, very low-certainty evidence). Prabhakaran 2019 measured depression scores at follow-up using the Patient Health Questionnaire-9 and reported no difference between groups (MD -1.6; 95%CI -4.4 to 1.2; n=3324, very low-certainty evidence).

Quality of life: Results from one RCT[43] suggest that interventions to promote integrated care compared to usual care may make little or no difference to quality of life, but the evidence is very uncertain. The RCT reported on the change in health-related quality of life from baseline to follow-up using the EuroQol-5D visual analogue scale and the EuroQol-5D index score. There was no difference between groups, neither for the Euro-Qol-5D visual analogue scale (MD 6.06; 95%CI -3.25 to 15.36; n=3969, very low- certainty evidence) nor for the EuroQol-5D index score (MD 0.00; 95%CI -0.05 to 0.06; n=3969, very low-certainty evidence).

Table 4: Summary of findings for interventions to promote integrated delivery of care compared to usual care for diabetes and hypertension in LMICs

Patient or population: Patients with diabetes, hypertension and other chronic diseases
Setting: Low- and middle-income countries
Intervention: Strategies to promote integrated care
Comparison: Usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care	Risk with Strategies to promote integrated care				
Mortality	29 per 1,000	**32 per 1,000** (23 to 45)	**RR 1.11** (0.79 to 1.56)	4393 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	Integrated care compared to usual care may make little or no difference to the risk of death, but the evidence is very uncertain
Depression	10-item Center for Epidemiologic Studies Depression Scale: MD −0.12 (−1.72 to 1.48) Patient Health Questionnaire-9: MD -1.6 (-4.4 to 1.2)			7293 (2 RCTs)	⊕◯◯◯ VERY LOW [a,b,c]	Integrated care compared to usual care may make little or no difference to depression scores, but the evidence is very uncertain
Change in quality of life (Euro-Qol-5D visual analogue scale)	Quality of life scores with usual care improved by a mean of 6.4 points	The mean change in quality of life with integrated care was **6.06 points higher** (3.25 points lower to 15.36 points higher)	-	3969 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	Integrated care compared to usual care may make little or no difference in quality of life, but the evidence is very uncertain
Change in HbA1c	The mean change in HbA1c with usual care ranged from -0.58 to -0.2%	The mean change in HbA1c with integrated care was **0.11 % higher** (0.2 lower to 0.42 higher)	-	1687 (2 RCTs)	⊕⊕◯◯ LOW [a,c]	Integrated care compared to usual care may have little or no effect on HbA1c
Change in systolic BP	The mean change in systolic BP with usual care ranged from -13.7 to -1.1 mmHg	The mean change in BP with integrated care was **1.11 mmHg higher** (1.14 lower to 3.35 higher)	-	4807 (2 RCTs)	⊕⊕◯◯ LOW [a,c]	Integrated care compared to usual care may have little or no effect on systolic BP

Change in total cholesterol	The mean change in total cholesterol with usual care was 2.0 mg/dl	The mean change in total cholesterol with integrated care was **2.5 mg/dl lower** (7.1 lower to 2.1 higher)	-	3324 (1 RCT)	⨁⨁◯◯ LOW [a,c]	Integrated care compared to usual care may have little or no effect on total cholesterol levels

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **BP**: Blood pressure; **HbA1c**: Glycated haemoglobin; **RCT**: Randomised controlled trial
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Footnotes: Explanation of GRADE certainty of evidence

a. Downgraded by 1 due to study limitations: high risk of performance bias and unclear risk of bias in some other domains
b. Downgraded by 1 due to imprecision: study not adequately powered for this outcome, small sample size and wide 95% CI
c. Downgraded by 1 due to indirectness: The interventions comprised strategies to promote integrated care at clinic level, and not integrated models of healthcare delivery at health system level

HbA1C: Results from two cluster RCTs[43 44] suggest that interventions to promote integrated care compared to usual care may have little or no effect on change in HbA1c from baseline to follow-up (MD 0.11%; 95%CI -0.20 to 0.42; n=1687; 2 RCTs, low-certainty evidence).

Systolic BP: Results from two cluster RCTs[43 44] suggest that interventions to promote integrated care compared to usual care may have little or no effect on change in systolic BP from baseline to follow-up (MD 1.11mmHg; 95%CI -1.41 to 3.35; n=4807; 2 RCTs, low-certainty evidence).

Total cholesterol: Results from one cluster RCT[44] suggest that interventions to promote integrated care compared to usual care may have little or no effect on change in total cholesterol from baseline to follow-up (MD -2.50mg/dl; 95%CI -7.10 to 2.10; n=3324; low-certainty evidence).

Retention in care: Fairall 2016 reported the number of clinic visits three months before the follow-up interview and found no difference between groups (incidence rate ratio 1.02; 95%CI 0.93 to 1.13; n=3121).

Adherence: One cluster RCT reported absolute numbers for drug adherence during the past seven days.[44] Patients in the intervention group reported greater adherence for both hypertensive drugs (833/1027; 81.1% vs. 648/1119; 57.9%) and anti-hyperglycemic drugs (683/829; 82.4% vs. 570/827; 68.9%) compared to patients receiving usual care.

Quality of care: One cluster RCT[44] reported on perceived change in quality of care as a composite perception on availability of drugs, guidance from physicians, quality of care, frequency of blood pressure measurement, and care provided by NCD nurses. Perceived quality of care improved in both groups. Patients receiving integrated care (n=1637), reported that quality of care was slightly/much better (96.6%), about the same (3.3%) and somewhat/much worse (0.2%). Patients receiving usual

care (n=1687) reported that quality of care was slightly/much better (95%), about the same (4.4%) and somewhat/much worse (0.5%).

Neither of the two cluster RCTs included in this comparison reported on access to care, continuity of care or cost of care.

Discussion

Summary of main results

We included five studies and two comparisons in this review. Three studies were conducted in South Africa, one in India and one in Kenya and Uganda. Two ITS studies and one cluster RCT provided data for the first comparison, integrated models of care compared to usual care. Results suggest that integrated models of care compared to usual care may make little or no difference to mortality, the number of people achieving BP or diabetes control, and access to care; may increase the number of people who achieve both HIV and BP/diabetes control; and may have a very small effect on achieving HIV control. However, the evidence for all outcomes is very uncertain. Two cluster RCTs provided data for the second comparison, interventions to promote integrated delivery of care compared to usual care. Results suggest that interventions to promote integrated delivery of care compared to usual care may make little or no difference to mortality, depression and quality of life, but the evidence is very uncertain. Interventions to promote integrated delivery of care compared to usual care may have little or no effect on HbA1c, systolic BP, and total cholesterol levels. Process outcomes were poorly reported across included studies, with none of the studies reporting on continuity of care or cost of care.

Agreements and disagreements with other reviews

Other systematic reviews that assessed the effects of integrated models of care on health outcomes in LMICs had similar findings. Dudley and Garner[30] assessed strategies to integrate PHC services on healthcare delivery and health status in LMICs. They found no evidence that integrated services improved healthcare delivery or health status. However, none of the included studies assessed integrated care for NCDs. Haldane and colleagues[28] described existing integrated models of care for HIV and NCDs and assessed health outcomes, barriers and facilitators. However, most of the included studies were descriptive or observational and health outcomes were poorly reported. Indeed, they highlighted the need for rigorous research that includes long-term follow-up and the role of incentives.

Overall completeness and applicability of evidence

Although we considered multi-morbidity in terms of diabetes and/or hypertension plus any other disease, four out of five studies were conducted in sub-Saharan Africa and included people with diabetes and/or hypertension (and other NCDs) and HIV. All studies were conducted in rural settings. Due to successful transformation of the health systems to deliver HIV programmes, sub-Saharan Africa is presented with a unique opportunity to leverage the investments made in order to scale-up NCD services. This can be achieved in various ways, such as integrating NCD services into facilities originally providing HIV care only, integrating HIV care into PHC facilities that offer NCD care, or concurrent introduction of HIV and NCD services.[8] However, even though this is recognised, there are still questions linked to the implementation of integrated models of care. In South Africa, the ICDM model, the intervention evaluated in the ITS study by Ameh and colleagues,[42] is one example where the vertical HIV programme was integrated into general PHC facilities. As part of the pilot programme, Ameh and colleagues not only evaluated the impact on health outcomes, but also conducted a qualitative study to explore the perspectives of healthcare providers and patients on the

quality of care in the ICDM model.[53] They found that PHC facilities experienced BP drug stock-outs, lack of functioning BP machines and staff shortages, among others, which impacted on the delivery of care and indirectly therefore on the health outcomes. Integrated NCD and HIV care is implemented to a varying degree in other sub-Saharan African countries. A study examining policies and programmes for integrated HIV and NCD care in Malawi, Kenya, South Africa and Swaziland found that these countries still experience challenges in implementing integrated care. Some of these are related to inadequate data to determine the burden of NCDs among PLHIV at a local level, lack of evidence to support the implementation of integrated care models, inadequate stakeholder engagement, lack of NCD care capacity and other health system challenges.[54]

Our definition of integrated care was based on a "one-stop-shop" model whereby a patient receives all necessary care or services under one roof by one or more health-care professional (Figure 1), which is just one way of describing integrated care. Indeed, a narrative review by Njuguna, et al. [55] aimed to describe various models of integrated care for HIV and NCDs in sub-Saharan Africa. Based on the definition by WHO, the authors defined integrated care as the "coordination, co-location, or simultaneous delivery of HIV and NCD services to patients who need it, when they need it" and identified five models. These include community-based integrated HIV and NCD screening in the general population; screening for NCD risk factors among PLHIV; integrated care for HIV and NCDs in healthcare facilities through leveraging the HIV infrastructure to manage NCDs; differential care for people well-controlled HIV or NCDs, which includes longer follow-up periods for stable patients; and population health for all patients with any need.[55]

Strengths and limitations

We followed a rigorous and systematic process according to standard systematic review methods. We performed a comprehensive search of published and unpublished studies up to 12 December 2019, with no language restrictions. We purposefully included study designs that are able to provide reliable evidence on the effects of integrated care on health and process outcomes, and followed guidance provided by Cochrane EPOC. We assessed the certainty of evidence using the GRADE approach across outcomes, taking into consideration study limitations, inconsistency, imprecision, publication bias and indirectness when downgrading the certainty of evidence.

Integration of care for NCDs and HIV or other diseases is complex, partly due to the complex nature of health systems.[56] We aimed to compare fully integrated models of care to partially integrated models of care or stand-alone care. However, it was difficult to classify interventions according to our pre-specified definitions and we thus lumped interventions that integrated service delivery as 'integrated models of care'. We included two cluster RCTs that aimed to promote integrated delivery of care through clinical management tools, which is different from integrated care at facility level. We discussed this within our team and concluded that the aim of these interventions was to provide care in a holistic way and to address all the needs of an individual when s/he presents to a healthcare facility, and thus met our eligibility criteria. Furthermore, included studies did not provide adequate information on the level of integration in comparisons, but rather referred to these as standard or usual care. While these referred a lesser degree of integration compared to the interventions, we were not able to categorise these as either partially integrated care or stand-alone care.

Our review focused on the effectiveness of integrating care for people with diabetes, hypertension and other co-morbidities in terms of health outcomes, which is just one question that needs to be answered. In other words, the question of our review focused on one building block of health systems as described by the WHO.[56] Although we aimed to examine process outcomes, these were limited to access to care, retention in care, adherence, continuity of care, quality of care and cost of care; and were poorly reported across included studies. The scope of our review did not include outcomes related to implementation or perspectives from health providers and patients, which are

important aspects to consider. Although the literature predominantly highlights the need to integrate NCD and HIV care, integrating mental health services into existing NCD and or HIV services is just as important. Four[48-51] of the five ongoing studies that we identified examine integration of mental health with NCDs.

Conclusion

The evidence on the effectiveness of integrated models of care for people with diabetes, hypertension and other co-morbidities, on health outcomes is very uncertain. We therefore do not know whether integrated models of care lead to better or worse outcomes, or may make no difference at all among people with diabetes, hypertension and other chronic conditions. There is a need to scale-up NCD services, particularly in LMICs. In the context of an increasing burden of NCDs against a backdrop of other chronic diseases, and scarce health system resources, such as human capacity and funding, policies and programmes need to promote integrated models of care and holistic, patient-centred services. However, these need to take into consideration context-specific factors related to the health system and the targeted population.

Further rigorous studies assessing the effects of integrated models of care on health outcomes are needed. These studies should include an adequate description of the integrated model of care, assess long term health effects as well as patient important outcomes, and cost of care. Furthermore, there is a need to conduct implementation research, economic evaluations as well as qualitative research on the barriers and facilitators to integrated models of care at patient and health-system level in order to guide policy makers in planning and allocation of resources in order to maximise the potential benefits of integrated care as well strengthening the health systems in achieving universal health coverage in LMICs.

Authors' contributions

All authors contributed to development of the review protocol. JUN and AR screened titles and abstracts; JUN, AR, TY and CMB participated in full text screening; TY, JJM and IT helped to resolve discrepancies. AR, JUN and IT extracted data and assessed risk of bias. AR and IT assessed certainty of evidence with input from TY and JJM. TY and JJM provided overall methodological guidance. JUN drafted the background section, AR drafted the rest of the manuscript. JUN, IT, TY, and CMB critically read and revised the manuscript. All authors have approved the final version of the manuscript.

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Ethics approval

This systematic review does not involve human participants. All data included is in the public domain and ethics approval was thus not sought.

Data sharing statement

All data relevant to the study are included in the article or uploaded as supplementary information.

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Competing interests statement

All authors have no known conflict of interest.

Protocol

Uwimana Nicol J, Rohwer A, Young T, et al. Integrated models of care for diabetes and hypertension in low- and middle-income countries (LMICs): Protocol for a systematic review. *Syst Rev* 2018;7(1):203. doi: 10.1186/s13643-018-0865-8 [published Online First: 2018/11/22]

Figures

Figure 1: Logic model of integrated care

Figure 2: PRISMA flow diagram

Figure 3: Risk of bias in ITS studies

Figure 4: Risk of bias for cluster RCTs

Supplementary files

Supplementary file 1: Search strategies for all databases

Supplementary file 2: Table of excluded studies

Supplementary file 3: Summary of interventions according to the TIDiER checklist: Integrated models of care

Supplementary file 4: Summary of interventions according to the TIDiER checklist: Interventions to promote integrated delivery of care

Supplementary file 5: Risk of bias assessments for included studies

Supplementary file 6: Forest plots

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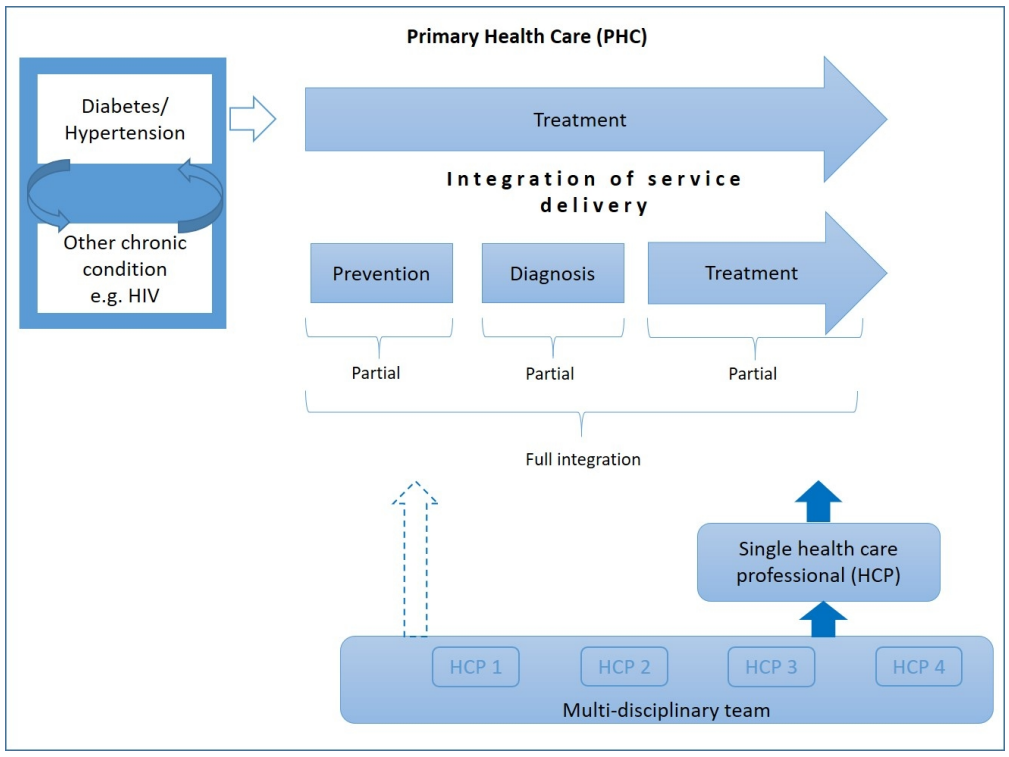

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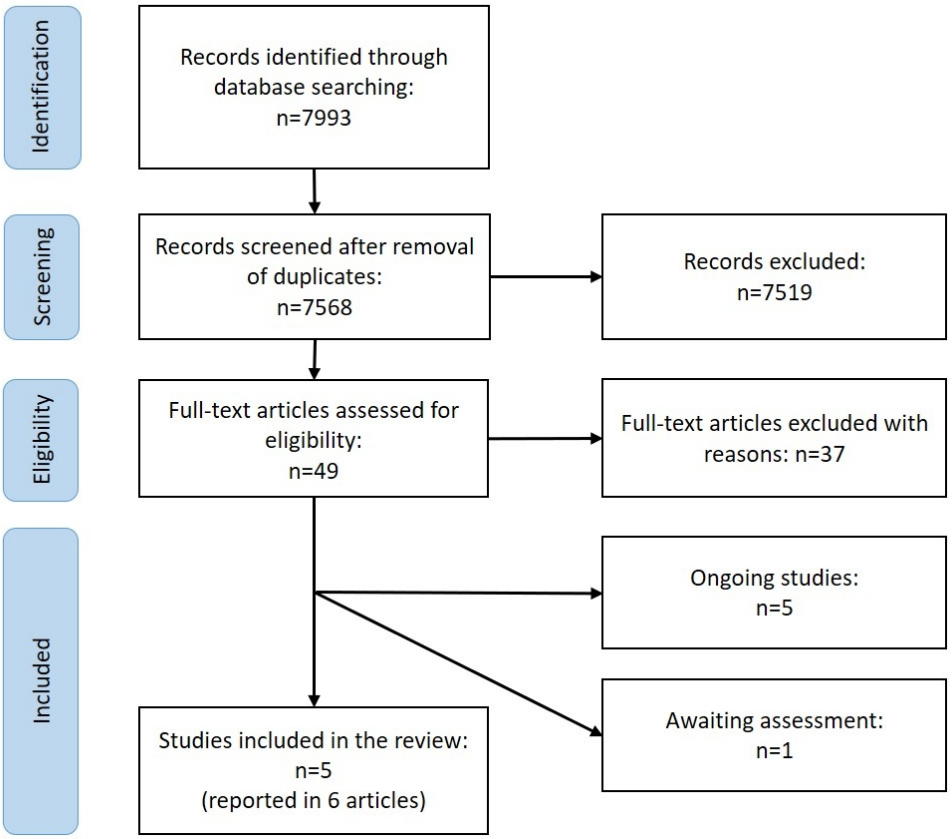

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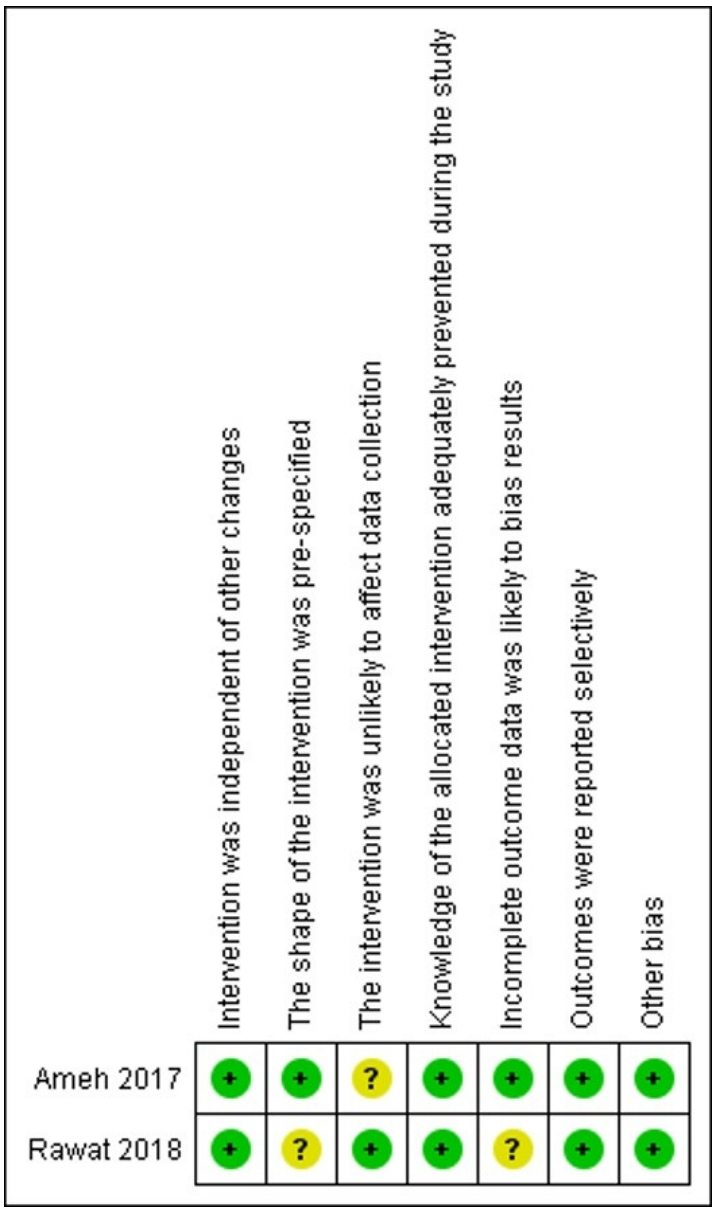

44x75mm (300 x 300 DPI)

98x73mm (300 x 300 DPI)

Supplementary file 1: Search strategies for electronic databases

1. Medline (PubMed) search strategy

#1 "Hypertension"[Mesh] OR (hypertension OR hypertention OR "blood pressure" OR “arterial pressure” OR systolic OR diastolic)[title/abstract]

#2 diabetes OR "diabetes mellitus")[title/abstract] OR "Diabetes Mellitus"[Mesh])

#3 #1 OR #2

#4 (dyslipidaemia OR dyslipidemia OR cholesterol OR LDL OR HDL OR triglyceride OR triglycerides OR low density lipoprotein OR high density lipoprotein OR low-density lipoprotein OR high-density lipoprotein)[title/abstract] OR "Dyslipidemias"[Mesh]

#5 ((((HIV OR hiv-1 OR hiv-2* OR hiv1 OR hiv2 OR hiv infect* OR human immunodeficiency virus OR human immune deficiency virus OR human immuno-deficiency virus OR human immune-deficiency virus OR ((human immun*) AND (deficiency virus)) OR acquired immunodeficiency syndromes OR acquired immune deficiency syndrome OR acquired immuno-deficiency syndrome OR acquired immune-deficiency syndrome OR ((acquired immun*) AND (deficiency syndrome)) OR HIV/AIDS)))) OR ((HIV infections [MeSH] OR HIV [MeSH]))

#6 (tuberculosis OR tuberculoses OR tb)[Title/Abstract] OR "tuberculosis"[Mesh]

#7 "noncommunicable disease" OR "noncommunicable diseases" OR "non-communicable disease" OR "non-communicable diseases" OR NCD OR NCDs OR "Noncommunicable Diseases"[Mesh]

#8 (comorbid* OR co-morbid* OR "co morbidity" OR multimorbidity OR multi-morbid OR "multi morbidity")[title/abstract] OR "Multimorbidity"[Mesh] OR "Comorbidity"[Mesh]

#9 multi-disease* OR multidisease* OR multi disease* OR multiple condition* OR multi-condition* OR multi condition* OR multiple illness* OR multi-illness* OR multi illness* OR multiple syndrome* OR multi-syndrome* OR multi syndrome* OR concurrent condition* OR concurrent illness* OR concurrent disease* OR co-existing disease* OR coexisting disease* OR co-existing illness* OR coexisting illness* OR co-existing syndrome* OR coexisting syndrome* OR co-existing condition* OR coexisting condition* OR co-occurring disease* OR co occuring disease* OR cooccuring disease* OR co-occurring illness* OR co occurring illness* OR cooccurring illness* OR co-occurring syndrome* OR co occurring syndrome* OR cooccurring syndrome* OR co-occurring condition* OR co occurring condition* OR cooccurring condition*

#10 chronic disease* OR lifestyle disease* OR "diseases of lifestyle" OR "disease of lifestyle" OR "Multiple Chronic Conditions"[Mesh] OR "Chronic Disease"[Mesh]

#11 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

#12 "Delivery of Health Care, Integrated"[Mesh] OR “delivery of care” OR “delivery of health” OR "delivery of healthcare" OR "Comprehensive Health Care"[Mesh] OR "comprehensive healthcare" OR "comprehensive care" OR "comprehensive health" OR "Continuity of Patient Care"[Mesh] OR "continuity of patient care" OR "continuity of care" OR "continuity of health" OR "continuity of healthcare" OR "Patient-Centered Care"[Mesh] OR "patient centered care" OR "patient centred care"

#13 "Referral and Consultation"[Mesh] OR (referral AND consultation)

#14 integrat* care OR "integration of care" OR integrat* services OR "integration of services" OR integrat* programmes OR integrat* programs OR “integration of programmes” OR “integration of programs” OR integrat* service delivery OR “integration of service delivery” OR integrat* services OR “integration of services” OR integrat* delivery OR integrat* management OR “integration of management”

#15 coordinat* care OR "coordination of care" OR coordinat* services OR "coordination of services" OR coordinat* programmes OR coordinat* programs OR “coordination of programmes” OR “coordination of programs” OR coordinat* service delivery OR “coordination of service delivery” OR coordinat* services OR “coordination of services” OR coordinat* delivery OR coordinat* management OR “coordination of management”

#16 co-ordinat* care OR "co-ordination of care" OR co-ordinat* services OR "co-ordination of services" OR co-ordinat* programmes OR co-ordinat* programs OR “co-ordination of programmes” OR “co-ordination of programs” OR co-ordinat* service delivery OR “co-ordination of service delivery” OR co-ordinat* services OR “co-ordination of services” OR co-ordinat* delivery OR co-ordinat* management OR “co-ordination of management”

#17 horizontal care OR vertical care OR horizontal services OR vertical services OR horizontal programmes OR horizontal programs OR vertical programmes OR vertical programs OR horizontal service delivery OR vertical service delivery OR horizontal services OR vertical services OR horizontal delivery OR vertical management OR vertical management

#18 “multi team” OR multiteam “multi care” OR multicare OR “multi clinic” OR multiclinic OR “multi service” OR multiservice OR “multi program” OR multiprogram OR “multi programme” OR “multi delivery” OR multidelivery OR “multi management”

#19 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18

#20 #3 AND #11 AND #19

#21 Developing Countries[Mesh:noexp] OR Africa[Mesh:noexp] OR Africa, Northern[Mesh:noexp] OR Africa South of the Sahara[Mesh:noexp] OR Africa, Central[Mesh:noexp] OR Africa, Eastern[Mesh:noexp] OR Africa, Southern[Mesh:noexp] OR Africa, Western[Mesh:noexp] OR Asia[Mesh:noexp] OR Asia, Central[Mesh:noexp] OR Asia, Southeastern[Mesh:noexp] OR Asia, Western[Mesh:noexp] OR Caribbean Region[Mesh:noexp] OR West Indies[Mesh:noexp] OR South America[Mesh:noexp] OR Latin America[Mesh:noexp] OR Central America[Mesh:noexp] OR Afghanistan[Mesh:noexp] OR Albania[Mesh:noexp] OR Algeria[Mesh:noexp] OR American Samoa[Mesh:noexp] OR Angola[Mesh:noexp] OR "Antigua and Barbuda"[Mesh:noexp] OR Argentina[Mesh:noexp] OR Armenia[Mesh:noexp] OR Azerbaijan[Mesh:noexp] OR Bahrain[Mesh:noexp] OR Bangladesh[Mesh:noexp] OR Barbados[Mesh:noexp] OR Benin[Mesh:noexp] OR Byelarus[Mesh:noexp] OR Belize[Mesh:noexp] OR Bhutan[Mesh:noexp] OR Bolivia[Mesh:noexp] OR Bosnia-Herzegovina[Mesh:noexp] OR Botswana[Mesh:noexp] OR Brazil[Mesh:noexp] OR Bulgaria[Mesh:noexp] OR Burkina Faso[Mesh:noexp] OR Burundi[Mesh:noexp] OR Cambodia[Mesh:noexp] OR Cameroon[Mesh:noexp] OR Cape Verde[Mesh:noexp] OR Central African Republic[Mesh:noexp] OR Chad[Mesh:noexp] OR Chile[Mesh:noexp] OR China[Mesh:noexp] OR Colombia[Mesh:noexp] OR Comoros[Mesh:noexp] OR Congo[Mesh:noexp] OR Costa Rica[Mesh:noexp] OR Cote d'Ivoire[Mesh:noexp] OR Croatia[Mesh:noexp] OR Cuba[Mesh:noexp] OR Cyprus[Mesh:noexp] OR Czechoslovakia[Mesh:noexp] OR Czech Republic[Mesh:noexp] OR Slovakia[Mesh:noexp] OR Djibouti[Mesh:noexp] OR "Democratic Republic of the Congo"[Mesh:noexp] OR

Dominica[Mesh:noexp] OR Dominican Republic[Mesh:noexp] OR East Timor[Mesh:noexp] OR Ecuador[Mesh:noexp] OR Egypt[Mesh:noexp] OR El Salvador[Mesh:noexp] OR Eritrea[Mesh:noexp] OR Estonia[Mesh:noexp] OR Ethiopia[Mesh:noexp] OR Fiji[Mesh:noexp] OR Gabon[Mesh:noexp] OR Gambia[Mesh:noexp] OR "Georgia (Republic)"[Mesh:noexp] OR Ghana[Mesh:noexp] OR Greece[Mesh:noexp] OR Grenada[Mesh:noexp] OR Guatemala[Mesh:noexp] OR Guinea[Mesh:noexp] OR Guinea-Bissau[Mesh:noexp] OR Guam[Mesh:noexp] OR Guyana[Mesh:noexp] OR Haiti[Mesh:noexp] OR Honduras[Mesh:noexp] OR Hungary[Mesh:noexp] OR India[Mesh:noexp] OR Indonesia[Mesh:noexp] OR Iran[Mesh:noexp] OR Iraq[Mesh:noexp] OR Jamaica[Mesh:noexp] OR Jordan[Mesh:noexp] OR Kazakhstan[Mesh:noexp] OR Kenya[Mesh:noexp] OR Korea[Mesh:noexp] OR Kosovo[Mesh:noexp] OR Kyrgyzstan[Mesh:noexp] OR Laos[Mesh:noexp] OR Latvia[Mesh:noexp] OR Lebanon[Mesh:noexp] OR Lesotho[Mesh:noexp] OR Liberia[Mesh:noexp] OR Libya[Mesh:noexp] OR Lithuania[Mesh:noexp] OR Macedonia[Mesh:noexp] OR Madagascar[Mesh:noexp] OR Malaysia[Mesh:noexp] OR Malawi[Mesh:noexp] OR Mali[Mesh:noexp] OR Malta[Mesh:noexp] OR Mauritania[Mesh:noexp] OR Mauritius[Mesh:noexp] OR Mexico[Mesh:noexp] OR Micronesia[Mesh:noexp] OR Middle East[Mesh:noexp] OR Moldova[Mesh:noexp] OR Mongolia[Mesh:noexp] OR Montenegro[Mesh:noexp] OR Morocco[Mesh:noexp] OR Mozambique[Mesh:noexp] OR Myanmar[Mesh:noexp] OR Namibia[Mesh:noexp] OR Nepal[Mesh:noexp] OR Netherlands Antilles[Mesh:noexp] OR New Caledonia[Mesh:noexp] OR Nicaragua[Mesh:noexp] OR Niger[Mesh:noexp] OR Nigeria[Mesh:noexp] OR Oman[Mesh:noexp] OR Pakistan[Mesh:noexp] OR Palau[Mesh:noexp] OR Panama[Mesh:noexp] OR Papua New Guinea[Mesh:noexp] OR Paraguay[Mesh:noexp] OR Peru[Mesh:noexp] OR Philippines[Mesh:noexp] OR Poland[Mesh:noexp] OR Portugal[Mesh:noexp] OR Puerto Rico[Mesh:noexp] OR Romania[Mesh:noexp] OR Russia[Mesh:noexp] OR "Russia (Pre-1917)"[Mesh:noexp] OR Rwanda[Mesh:noexp] OR "Saint Kitts and Nevis"[Mesh:noexp] OR Saint Lucia[Mesh:noexp] OR "Saint Vincent and the Grenadines"[Mesh:noexp] OR Samoa[Mesh:noexp] OR Saudi Arabia[Mesh:noexp] OR Senegal[Mesh:noexp] OR Serbia[Mesh:noexp] OR Montenegro[Mesh:noexp] OR Seychelles[Mesh:noexp] OR Sierra Leone[Mesh:noexp] OR Slovenia[Mesh:noexp] OR Sri Lanka[Mesh:noexp] OR Somalia[Mesh:noexp] OR South Africa[Mesh:noexp] OR Sudan[Mesh:noexp] OR Suriname[Mesh:noexp] OR Swaziland[Mesh:noexp] OR Syria[Mesh:noexp] OR Tajikistan[Mesh:noexp] OR Tanzania[Mesh:noexp] OR Thailand[Mesh:noexp] OR Togo[Mesh:noexp] OR Tonga[Mesh:noexp] OR "Trinidad and Tobago"[Mesh:noexp] OR Tunisia[Mesh:noexp] OR Turkey[Mesh:noexp] OR Turkmenistan[Mesh:noexp] OR Uganda[Mesh:noexp] OR Ukraine[Mesh:noexp] OR Uruguay[Mesh:noexp] OR USSR[Mesh:noexp] OR Uzbekistan[Mesh:noexp] OR Vanuatu[Mesh:noexp] OR Venezuela[Mesh:noexp] OR Vietnam[Mesh:noexp] OR Yemen[Mesh:noexp] OR Yugoslavia[Mesh:noexp] OR Zambia[Mesh:noexp] OR Zimbabwe[Mesh:noexp]

#22 Macedonia[tw] OR Madagascar[tw] OR Malagasy Republic[tw] OR Malaysia[tw] OR Malaya[tw] OR Malay[tw] OR Sabah[tw] OR Sarawak[tw] OR Malawi[tw] OR Nyasaland[tw] OR Mali[tw] OR Malta[tw] OR Marshall Islands[tw] OR Mauritania[tw] OR Mauritius[tw] OR Agalega Islands[tw] OR Mexico[tw] OR Micronesia[tw] OR Middle East[tw] OR Moldova[tw] OR Moldovia[tw] OR Moldovian[tw] OR Mongolia[tw] OR Montenegro[tw] OR Morocco[tw] OR Ifni[tw] OR Mozambique[tw] OR Myanmar[tw] OR Myanma[tw] OR Burma[tw] OR Namibia[tw] OR Nepal[tw] OR Netherlands Antilles[tw] OR New Caledonia[tw] OR Nicaragua[tw] OR Niger[tw] OR Nigeria[tw] OR Northern Mariana Islands[tw] OR Oman[tw] OR Muscat[tw] OR Pakistan[tw] OR Palau[tw] OR Palestine[tw] OR Panama[tw] OR Paraguay[tw] OR Peru[tw] OR Philippines[tw] OR Philipines[tw] OR Phillipines[tw] OR Phillippines[tw] OR Poland[tw] OR Portugal[tw] OR Puerto Rico[tw] OR Romania[tw] OR Rumania[tw] OR Roumania[tw] OR Russia[tw] OR Russian[tw] OR Rwanda[tw] OR Ruanda[tw] OR Saint Kitts[tw] OR St Kitts[tw] OR Nevis[tw] OR Saint Lucia[tw] OR St Lucia[tw] OR Saint Vincent[tw] OR St Vincent[tw] OR Grenadines[tw] OR Samoa[tw] OR Samoan Islands[tw] OR

Navigator Island[tw] OR Navigator Islands[tw] OR Sao Tome[tw] OR Saudi Arabia[tw] OR Senegal[tw] OR Serbia[tw] OR Montenegro[tw] OR Seychelles[tw] OR Sierra Leone[tw] OR Slovenia[tw] OR Sri Lanka[tw] OR Ceylon[tw] OR Solomon Islands[tw] OR Somalia[tw] OR Sudan[tw] OR Suriname[tw] OR Surinam[tw] OR Swaziland[tw] OR Syria[tw] OR Tajikistan[tw] OR Tadzhikistan[tw] OR Tadjikistan[tw] OR Tadzhik[tw] OR Tanzania[tw] OR Thailand[tw] OR Togo[tw] OR Togolese Republic[tw] OR Tonga[tw] OR Trinidad[tw] OR Tobago[tw] OR Tunisia[tw] OR Turkey[tw] OR Turkmenistan[tw] OR Turkmen[tw] OR Uganda[tw] OR Ukraine[tw] OR Uruguay[tw] OR USSR[tw] OR Soviet Union[tw] OR Union of Soviet Socialist Republics[tw] OR Uzbekistan[tw] OR Uzbek OR Vanuatu[tw] OR New Hebrides[tw] OR Venezuela[tw] OR Vietnam[tw] OR Viet Nam[tw] OR West Bank[tw] OR Yemen[tw] OR Yugoslavia[tw] OR Zambia[tw] OR Zimbabwe[tw] OR Rhodesia[tw]

#23 Africa[tw] OR Asia[tw] OR Caribbean[tw] OR West Indies[tw] OR South America[tw] OR Latin America[tw] OR Central America[tw] OR Afghanistan[tw] OR Albania[tw] OR Algeria[tw] OR Angola[tw] OR Antigua[tw] OR Barbuda[tw] OR Argentina[tw] OR Armenia[tw] OR Armenian[tw] OR Aruba[tw] OR Azerbaijan[tw] OR Bahrain[tw] OR Bangladesh[tw] OR Barbados[tw] OR Benin[tw] OR Byelarus[tw] OR Byelorussian[tw] OR Belarus[tw] OR Belorussian[tw] OR Belorussia[tw] OR Belize[tw] OR Bhutan[tw] OR Bolivia[tw] OR Bosnia[tw] OR Herzegovina[tw] OR Hercegovina[tw] OR Botswana[tw] OR Brasil[tw] OR Brazil[tw] OR Bulgaria[tw] OR Burkina Faso[tw] OR Burkina Fasso[tw] OR Upper Volta[tw] OR Burundi[tw] OR Urundi[tw] OR Cambodia[tw] OR Khmer Republic[tw] OR Kampuchea[tw] OR Cameroon[tw] OR Cameroons[tw] OR Cameron[tw] OR Camerons[tw] OR Cape Verde[tw] OR Central African Republic[tw] OR Chad[tw] OR Chile[tw] OR China[tw] OR Colombia[tw] OR Comoros[tw] OR Comoro Islands[tw] OR Comores[tw] OR Mayotte[tw] OR Congo[tw] OR Zaire[tw] OR Costa Rica[tw] OR Cote d'Ivoire[tw] OR Ivory Coast[tw] OR Croatia[tw] OR Cuba[tw] OR Cyprus[tw] OR Czechoslovakia[tw] OR Czech Republic[tw] OR Slovakia[tw] OR Slovak Republic[tw] OR Djibouti[tw] OR French Somaliland[tw] OR Dominica[tw] OR Dominican Republic[tw] OR East Timor[tw] OR East Timur[tw] OR Timor Leste[tw] OR Ecuador[tw] OR Egypt[tw] OR United Arab Republic[tw] OR El Salvador[tw] OR Eritrea[tw] OR Estonia[tw] OR Ethiopia[tw] OR Fiji[tw] OR Gabon[tw] OR Gabonese Republic[tw] OR Gambia[tw] OR Gaza[tw] OR Georgia Republic[tw] OR Georgian Republic[tw] OR Ghana[tw] OR Gold Coast[tw] OR Greece[tw] OR Grenada[tw] OR Guatemala[tw] OR Guinea[tw] OR Guam[tw] OR Guiana[tw] OR Guyana[tw] OR Haiti[tw] OR Honduras[tw] OR Hungary[tw] OR India[tw] OR Maldives[tw] OR Indonesia[tw] OR Iran[tw] OR Iraq[tw] OR Isle of Man[tw] OR Jamaica[tw] OR Jordan[tw] OR Kazakhstan[tw] OR Kazakh[tw] OR Kenya[tw] OR Kiribati[tw] OR Korea[tw] OR Kosovo[tw] OR Kyrgyzstan[tw] OR Kirghizia[tw] OR Kyrgyz Republic[tw] OR Kirghiz[tw] OR Kirgizstan[tw] OR "Lao PDR"[tw] OR Laos[tw] OR Latvia[tw] OR Lebanon[tw] OR Lesotho[tw] OR Basutoland[tw] OR Liberia[tw] OR Libya[tw] OR Lithuania[tw]

#24 "developing country"[tw] OR "developing countries"[tw] OR "developing nation"[tw] OR "developing nations"[tw] OR "developing population"[tw] OR "developing populations"[tw] OR "developing world"[tw] OR "less developed country"[tw] OR "less developed countries"[tw] OR "less developed nation"[tw] OR "less developed nations"[tw] OR "less developed population"[tw] OR "less developed populations"[tw] OR "less developed world"[tw] OR "lesser developed country"[tw] OR "lesser developed countries"[tw] OR "lesser developed nation"[tw] OR "lesser developed nations"[tw] OR "lesser developed population"[tw] OR "lesser developed populations"[tw] OR "lesser developed world"[tw] OR "under developed country"[tw] OR "under developed countries"[tw] OR "under developed nation"[tw] OR "under developed nations"[tw] OR "under developed population"[tw] OR "under developed populations"[tw] OR "under developed world"[tw] OR "underdeveloped country"[tw] OR "underdeveloped countries"[tw] OR "underdeveloped nation"[tw] OR "underdeveloped nations"[tw] OR "underdeveloped population"[tw] OR "underdeveloped populations"[tw] OR "underdeveloped world"[tw] OR "middle income country"[tw] OR "middle income countries"[tw] OR "middle income nation"[tw] OR "middle income nations"[tw] OR "middle income population"[tw] OR "middle income populations"[tw] OR "low income country"[tw] OR "low

income countries"[tw] OR "low income nation"[tw] OR "low income nations"[tw] OR "low income population"[tw] OR "low income populations"[tw] OR "lower income country"[tw] OR "lower income countries"[tw] OR "lower income nation"[tw] OR "lower income nations"[tw] OR "lower income population"[tw] OR "lower income populations"[tw] OR "underserved country"[tw] OR "underserved countries"[tw] OR "underserved nation"[tw] OR "underserved nations"[tw] OR "underserved population"[tw] OR "underserved populations"[tw] OR "underserved world"[tw] OR "under served country"[tw] OR "under served countries"[tw] OR "under served nation"[tw] OR "under served nations"[tw] OR "under served population"[tw] OR "under served populations"[tw] OR "under served world"[tw] OR "deprived country"[tw] OR "deprived countries"[tw] OR "deprived nation"[tw] OR "deprived nations"[tw] OR "deprived population"[tw] OR "deprived populations"[tw] OR "deprived world"[tw] OR "poor country"[tw] OR "poor countries"[tw] OR "poor nation"[tw] OR "poor nations"[tw] OR "poor population"[tw] OR "poor populations"[tw] OR "poor world"[tw] OR "poorer country"[tw] OR "poorer countries"[tw] OR "poorer nation"[tw] OR "poorer nations"[tw] OR "poorer population"[tw] OR "poorer populations"[tw] OR "poorer world"[tw] OR "developing economy"[tw] OR "developing economies"[tw] OR "less developed economy"[tw] OR "less developed economies"[tw] OR "lesser developed economy"[tw] OR "lesser developed economies"[tw] OR "under developed economy"[tw] OR "under developed economies"[tw] OR "underdeveloped economy"[tw] OR "underdeveloped economies"[tw] OR "middle income economy"[tw] OR "middle income economies"[tw] OR "low income economy"[tw] OR "low income economies"[tw] OR "lower income economy"[tw] OR "lower income economies"[tw] OR "low gdp"[tw] OR "low gnp"[tw] OR "low gross domestic"[tw] OR "low gross national"[tw] OR "lower gdp"[tw] OR "lower gnp"[tw] OR "lower gross domestic"[tw] OR "lower gross national"[tw] OR lmic[tw] OR lmics[tw] OR "third world"[tw] OR "lami country"[tw] OR "lami countries"[tw] OR "transitional country"[tw] OR "transitional countries"[tw]

#25 #21 OR #22 OR #23 OR #24

#26 #20 AND #25

2. CENTRAL

#1 MeSH descriptor: [Hypertension] explode all trees

#2 hypertension OR hypertention OR "blood pressure" OR “arterial pressure” OR systolic OR diastolic

#3 diabetes OR "diabetes mellitus"

#4 MeSH descriptor: [Diabetes Mellitus] explode all trees

#5 #1 OR #2 OR #3 OR #4

#6 dyslipidaemia OR dyslipidemia OR cholesterol OR LDL OR HDL OR triglyceride OR triglycerides OR "low density lipoprotein" OR "high density lipoprotein" OR "low-density lipoprotein" OR "high-density lipoprotein"

#7 MeSH descriptor: [Dyslipidemias] explode all trees

#8 HIV OR hiv-1 OR hiv-2* OR hiv1 OR hiv2 OR "hiv infection" OR "hiv infections" OR "human immunodeficiency virus" OR "human immune deficiency virus" OR "human immuno-deficiency virus" OR "human immune-deficiency virus"

#9 (human immun*) AND (deficiency virus)

#10 "acquired immunodeficiency syndromes" OR "acquired immune deficiency syndrome" OR "acquired immuno-deficiency syndrome" OR "acquired immune-deficiency syndrome"

#11 (acquired immun*) AND (deficiency syndrome)

#12 HIVAIDS

#13 MeSH descriptor: [HIV Infections] explode all trees

#14 MeSH descriptor: [HIV] explode all trees

#15 tuberculosis OR tuberculoses OR tb

#16 MeSH descriptor: [Tuberculosis] explode all trees

#17 "noncommunicable disease" OR "noncommunicable diseases" OR "non-communicable disease" OR "non-communicable diseases" OR NCD OR NCDs

#18 MeSH descriptor: [Noncommunicable Diseases] explode all trees

#19 comorbidity OR comorbidities OR comorbid OR co-morbid OR co-morbidity OR co-morbidities OR "co morbidity" OR multimorbidity OR multi-morbid OR "multi morbidity"

#20 MeSH descriptor: [Multimorbidity] explode all trees

#21 MeSH descriptor: [Comorbidity] explode all trees

#22 multi-disease* OR multidisease* OR multi disease* OR multiple condition* OR multi-condition* OR multi condition* OR multiple illness* OR multi-illness* OR multi illness* OR multiple syndrome* OR multi-syndrome* OR multi syndrome* OR concurrent condition* OR concurrent illness* OR concurrent disease* OR co-existing disease* OR coexisting disease* OR co-existing illness* OR coexisting illness* OR co-existing syndrome* OR coexisting syndrome* OR co-existing condition* OR coexisting condition* OR co-occurring disease* OR co occuring disease* OR cooccuring disease* OR co-occurring illness* OR co occurring illness* OR cooccurring illness* OR co-occurring syndrome* OR co occurring syndrome* OR cooccurring syndrome* OR co-occurring condition* OR co occurring condition* OR cooccurring condition*

#23 chronic disease* OR lifestyle disease* OR "diseases of lifestyle" OR "disease of lifestyle"

#24 MeSH descriptor: [Multiple Chronic Conditions] explode all trees

#25 MeSH descriptor: [Chronic Disease] explode all trees

#26 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25

#27 MeSH descriptor: [Delivery of Health Care, Integrated] explode all trees

#28 “delivery of care” OR “delivery of health” OR "delivery of healthcare"

#29 MeSH descriptor: [Comprehensive Health Care] explode all trees

#30 "comprehensive healthcare" OR "comprehensive care" OR "comprehensive health"

#31 MeSH descriptor: [Continuity of Patient Care] explode all trees 23230

#32 "continuity of patient care" OR "continuity of care" OR "continuity of health" OR "continuity of healthcare"

#33 MeSH descriptor: [Patient-Centered Care] explode all trees

#34 "patient centered care" OR "patient centred care"

#35 MeSH descriptor: [Referral and Consultation] explode all trees

#36 referral AND consultation

#37 integrat* care OR "integration of care" OR integrat* services OR "integration of services" OR integrat* programmes OR integrat* programs OR “integration of programmes” OR “integration of programs” OR integrat* service delivery OR “integration of service delivery” OR integrat* services OR “integration of services” OR integrat* delivery OR integrat* management OR “integration of management”

#38 coordinat* care OR "coordination of care" OR coordinat* services OR "coordination of services" OR coordinat* programmes OR coordinat* programs OR “coordination of programmes” OR “coordination of programs” OR coordinat* service delivery OR “coordination of service delivery” OR coordinat* services OR “coordination of services” OR coordinat* delivery OR coordinat* management OR “coordination of management”

#39 co-ordinat* care OR "co-ordination of care" OR co-ordinat* services OR "co-ordination of services" OR co-ordinat* programmes OR co-ordinat* programs OR “co-ordination of programmes” OR “co-ordination of programs” OR co-ordinat* service delivery OR “co-ordination of service delivery” OR co-ordinat* services OR “co-ordination of services” OR co-ordinat* delivery OR co-ordinat* management OR “co-ordination of management”

#40 "horizontal care" OR "vertical care" OR "horizontal services" OR "vertical services" OR "horizontal programmes" OR "horizontal programs" OR "vertical programmes" OR "vertical programs" OR "horizontal service delivery" OR "vertical service delivery" OR "horizontal services" OR "vertical services" OR "horizontal delivery" OR "vertical management" OR "vertical management"

#41 “multi team” OR multiteam “multi care” OR multicare OR “multi clinic” OR multiclinic OR “multi service” OR multiservice OR “multi program” OR multiprogram OR “multi programme” OR “multi delivery” OR multidelivery OR “multi management”

#42 #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41

#43 #5 AND #26 AND #42

#44 (Africa or Asia or Caribbean or "West Indies" or "South America" or "Latin America" or "Central America")

#45 (Afghanistan or Albania or Algeria or Angola or Antigua or Barbuda or Argentina or Armenia or Armenian or Aruba or Azerbaijan or Bahrain or Bangladesh or Barbados or Benin or Byelarus or Byelorussian or Belarus or Belorussian or Belorussia or Belize or Bhutan or Bolivia or Bosnia or Herzegovina or Hercegovina or Botswana or Brasil or Brazil or Bulgaria or "Burkina Faso" or "Burkina Fasso" or "Upper Volta" or Burundi or Urundi or Cambodia or "Khmer Republic" or Kampuchea or Cameroon or Cameroons or Cameron or Camerons or "Cape Verde" or "Central African Republic" or Chad or Chile or China or Colombia or Comoros or "Comoro Islands" or Comores or Mayotte or Congo or "Republic of Congo" or Zaire or "Costa Rica" or "Cote d'Ivoire" or "Ivory Coast" or Croatia or Cuba or Cyprus or Czechoslovakia or "Czech Republic" or Slovakia or "Slovak Republic")

#46 (Djibouti or "French Somaliland" or Dominica or "Dominican Republic" or "East Timor" or "East Timur" or "Timor Leste" or Ecuador or Egypt or "United Arab Republic" or "El Salvador" or Eritrea or Estonia or Ethiopia or Fiji or Gabon or "Gabonese Republic" or Gambia or Gaza or Georgia or Georgian or Ghana or "Gold Coast" or Greece or Grenada or Guatemala or Guinea or Guam or Guiana or Guyana or Haiti or Honduras or Hungary or India or Maldives or Indonesia or Iran or Iraq or "Isle of Man" or Jamaica or Jordan or Kazakhstan or Kazakh or Kenya or Kiribati or Korea or Kosovo or

Kyrgyzstan or Kirghizia or "Kyrgyz Republic" or Kirghiz or Kirgizstan or "Lao PDR" or Laos or Latvia or Lebanon or Lesotho or Basutoland or Liberia or Libya or Lithuania)

#47 (Macedonia or Madagascar or "Malagasy Republic" or Malaysia or Malaya or Malay or Sabah or Sarawak or Malawi or Nyasaland or Mali or Malta or "Marshall Islands" or Mauritania or Mauritius or "Agalega Islands" or Mexico or Micronesia or "Middle East" or Moldova or Moldovia or Moldovian or Mongolia or Montenegro or Morocco or Ifni or Mozambique or Myanmar or Myanma or Burma or Namibia or Nepal or "Netherlands Antilles" or "New Caledonia" or Nicaragua or Niger or Nigeria or "Northern Mariana Islands" or Oman or Muscat or Pakistan or Palau or Palestine or Panama or Paraguay or Peru or Philippines or Philipines or Phillipines or Phillippines or Poland or Portugal or "Puerto Rico")

#48 (Romania or Rumania or Roumania or Russia or Russian or Rwanda or Ruanda or "Saint Kitts" or "St Kitts" or Nevis or "Saint Lucia" or "St Lucia" or "Saint Vincent" or "St Vincent" or Grenadines or Samoa or "Samoan Islands" or "Navigator Island" or "Navigator Islands" or "Sao Tome" or "Saudi Arabia" or Senegal or Serbia or Montenegro or Seychelles or "Sierra Leone" or Slovenia or "Sri Lanka" or Ceylon or "Solomon Islands" or Somalia or Sudan or South-sudan or Suriname or Surinam or Swaziland or Syria or Tajikistan or Tadzhikistan or Tadjikistan or Tadzhik or Tanzania or Thailand or Togo or "Togolese Republic" or Tonga or Trinidad or Tobago or Tunisia or Turkey or Turkmenistan or Turkmen or Uganda or Ukraine or Uruguay or USSR or "Soviet Union" or "Union of Soviet Socialist Republics" or Uzbekistan or Uzbek or Vanuatu or "New Hebrides" or Venezuela or Vietnam or "Viet Nam" or "West Bank" or Yemen or Yugoslavia or Zambia or Zimbabwe or Rhodesia)

#49 (developing or less* NEXT developed or "under developed" or underdeveloped or "middle income" or low* NEXT income or underserved or "under served" or deprived or poor*) NEXT (countr* or nation* or population* or world)

#50 (developing or less* NEXT developed or "under developed" or underdeveloped or "middle income" or low* NEXT income) NEXT (economy or economies)

#51 low* NEXT (gdp or gnp or "gross domestic" or "gross national")

#52 (low NEAR/3 middle NEAR/3 countr*)

#53 (lmic or lmics or "third world" or "lami country" or "lami countries")

#54 ("transitional country" or "transitional countries")

#55 #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54

#56 #43 AND #55

3. Embase

1 integrated health care system/ or integrated health care.mp.

2 *patient care/

3 ("comprehensive healthcare" or "comprehensive care" or "Continuity of Patient Care" or "continuity of care" or "continuity of healthcare" or "Patient-Centered Care").ti.

4 ("comprehensive healthcare" or "comprehensive care" or "Continuity of Patient Care" or "continuity of care" or "continuity of healthcare" or "Patient-Centered Care").ab.

5 (referral and consultation).mp.

6 ((integrated or integration) adj2 (care or services or program* or delivery or management)).ab.

7 ((integrated or integration) adj2 (care or services or program* or delivery or management)).ti.

8 ((coordination or coordinated) adj2 (care or services or program* or delivery or management)).ti.

9 ((coordination or coordinated) adj2 (care or services or program* or delivery or management)).ab.

10 ((horizontal or vertical) adj2 (care or services or program* or delivery or management)).ab.

11 ((horizontal or vertical) adj2 (care or services or program* or delivery or management)).ti.

12 (Multiteam or multi-team or multi-care or multicare or multiclinic or multiservice or multi-program* or multidelivery or multi-management).ti. or (Multiteam or multi-team or multi-care or multicare or multiclinic or multiservice or multi-program* or multidelivery or multi-management).ab.

13 *health care delivery/

14 (delivery adj2 healthcare).mp.

15 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14

16 hypertension.mp. or *hypertension/

17 (hypertension or hypertention or "blood pressure" or "arterial pressure" or systolic or diastolic).ti. or (hypertension or hypertention or "blood pressure" or "arterial pressure" or systolic or diastolic).ab.

18 diabetes.mp. or diabetes mellitus/

19 exp Neoplasms/

20 cardiovascular disease/

21 "heart disease".ti. or "heart disease*".ab.

22 *kidney disease/

23 ("kidney failure" or "renal failure" or "chronic kidney disease" or "renal disease").ti. or ("kidney failure" or "renal failure" or "chronic kidney disease" or "renal disease").ab.

24 (dyslipidaemia or dyslipidemia or cholesterol or LDL or HDL or triglyceride or triglycerides or low density lipoprotein or high density lipoprotein or low-density lipoprotein or high-density lipoprotein).ti. or (dyslipidaemia or dyslipidemia or cholesterol or LDL or HDL or triglyceride or triglycerides or low density lipoprotein or high density lipoprotein or low-density lipoprotein or high-density lipoprotein).ab.

25 HIV infection.mp. or Human immunodeficiency virus infection/

26 tuberculosis/

27 non-communicable diseases.mp. or non communicable disease/

28 comorbidity.mp. or comorbidity/

29 multimorbidity.mp. or multiple chronic conditions/

30 (multi-disease* or multidisease* or multi disease* or multiple condition* or multi-condition* or multi condition* or multiple illness* or multi-illness* or multi illness* or multiple syndrome* or multi-syndrome* or multi syndrome* or concurrent condition* or concurrent illness* or concurrent

disease* or co-existing disease* or coexisting disease* or co-existing illness* or coexisting illness* or co-existing syndrome* or coexisting syndrome* or co-existing condition* or coexisting condition* or co-occurring disease* or co occuring disease* or cooccuring disease* or co-occurring illness* or co occurring illness* or cooccurring illness* or co-occurring syndrome* or co occurring syndrome* or cooccurring syndrome* or co-occurring condition* or co occurring condition* or cooccurring condition*).ti.

31 (multi-disease* or multidisease* or multi disease* or multiple condition* or multi-condition* or multi condition* or multiple illness* or multi-illness* or multi illness* or multiple syndrome* or multi-syndrome* or multi syndrome* or concurrent condition* or concurrent illness* or concurrent disease* or co-existing disease* or coexisting disease* or co-existing illness* or coexisting illness* or co-existing syndrome* or coexisting syndrome* or co-existing condition* or coexisting condition* or co-occurring disease* or co occuring disease* or cooccuring disease* or co-occurring illness* or co occurring illness* or cooccurring illness* or co-occurring syndrome* or co occurring syndrome* or cooccurring syndrome* or co-occurring condition* or co occurring condition* or cooccurring condition*).ab.

32 (chronic disease* or lifestyle disease*).mp.

33 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32

34 15 and 33

35 developing countries.mp. or developing country/

36 (Africa or Asia or Caribbean or West Indies or South America or Latin America or Central America).mp.

37 (Afghanistan or Albania or Algeria or Angola or Antigua or Barbuda or Argentina or Armenia or Armenian or Aruba or Azerbaijan or Bahrain or Bangladesh or Barbados or Benin or Byelarus or Byelorussian or Belarus or Belorussian or Belorussia or Belize or Bhutan or Bolivia or Bosnia or Herzegovina or Hercegovina or Botswana or Brazil or Bulgaria or Burkina Faso or Burkina Fasso or Upper Volta or Burundi or Urundi or Cambodia or Khmer Republic or Kampuchea or Cameroon or Cameroons or Cameron or Camerons or Cape Verde or Central African Republic or Chad or Chile or China or Colombia or Comoros or Comoro Islands or Comores or Mayotte or Congo or Zaire or Costa Rica or Cote d'Ivoire or Ivory Coast or Croatia or Cuba or Cyprus or Czechoslovakia or Czech Republic or Slovakia or Slovak Republic or Djibouti or French Somaliland or Dominica or Dominican Republic or East Timor or East Timur or Timor Leste or Ecuador or Egypt or United Arab Republic or El Salvador or Eritrea or Estonia or Ethiopia or Fiji or Gabon or Gabonese Republic or Gambia or Gaza or Georgia Republic or Georgian Republic or Ghana or Gold Coast or Greece or Grenada or Guatemala or Guinea or Guam or Guiana or Guyana or Haiti or Honduras or Hungary or India or Maldives or Indonesia or Iran or Iraq or Isle of Man or Jamaica or Jordan or Kazakhstan or Kazakh or Kenya or Kiribati or Korea or Kosovo or Kyrgyzstan or Kirghizia or Kyrgyz Republic or Kirghiz or Kirgizstan or Lao PDR or Laos or Latvia or Lebanon or Lesotho or Basutoland or Liberia or Libya or Lithuania or Macedonia or Madagascar or Malagasy Republic or Malaysia or Malaya or Malay or Sabah or Sarawak or Malawi or Nyasaland or Mali or Malta or Marshall Islands or Mauritania or Mauritius or Agalega Islands or Mexico or Micronesia or Middle East or Moldova or Moldovia or Moldovian or Mongolia or Montenegro or Morocco or Ifni or Mozambique or Myanmar or Myanma or Burma or Namibia or Nepal or Netherlands Antilles or New Caledonia or Nicaragua or Niger or Nigeria or Northern Mariana Islands or Oman or Muscat or Pakistan or Palau or Palestine or Panama or Paraguay or Peru or Philippines or Philipines or Phillipines or Phillippines or Poland or Portugal or Puerto Rico or Romania or Rumania or Roumania or Russia or Russian or Rwanda or Ruanda or Saint Kitts or St Kitts or Nevis or Saint Lucia or St Lucia or Saint Vincent or St Vincent or Grenadines or Samoa or Samoan

Islands or Navigator Island or Navigator Islands or Sao Tome or Saudi Arabia or Senegal or Serbia or Montenegro or Seychelles or Sierra Leone or Slovenia or Sri Lanka or Ceylon or Solomon Islands or Somalia or Sudan or Suriname or Surinam or Swaziland or Syria or Tajikistan or Tadzhikistan or Tadjikistan or Tadzhik or Tanzania or Thailand or Togo or Togolese Republic or Tonga or Trinidad or Tobago or Tunisia or Turkey or Turkmenistan or Turkmen or Uganda or Ukraine or Uruguay or USSR or Soviet Union or Union of Soviet Socialist Republics or Uzbekistan or Uzbek or Vanuatu or New Hebrides or Venezuela or Vietnam or Viet Nam or West Bank or Yemen or Yugoslavia or Zambia or Zimbabwe or Rhodesia).mp.

38 ((developing or less* developed or under developed or underdeveloped or middle income or low* income or underserved or under served or deprived or poor*) adj (countr* or nation? or population? or world)).ab.

39 ((developing or less* developed or under developed or underdeveloped or middle income or low* income) adj (economy or economies)).ab. or ((developing or less* developed or under developed or underdeveloped or middle income or low* income) adj (economy or economies)).ti.

40 ((developing or less* developed or under developed or underdeveloped or middle income or low* income or underserved or under served or deprived or poor*) adj (countr* or nation? or population? or world)).ti.

41 (low* adj (gdp or gnp or gross domestic or gross national)).ti. or (low* adj (gdp or gnp or gross domestic or gross national)).ab.

42 (low adj3 middle adj3 countr*).ti. or (low adj3 middle adj3 countr*).ab.

43 (lmic or lmics or third world or lami countr*).ti. or (lmic or lmics or third world or lami countr*).ab.

44 transitional countr*.ti. or transitional countr*.ab.

45 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44

46 34 and 45

4. Web of Science (Core collection)

TOPIC: (hypertension OR hypertention OR "blood pressure" OR “arterial pressure” OR systolic OR diastolic OR diabetes OR "diabetes mellitus") AND TOPIC: (dyslipidaemia OR dyslipidemia OR cholesterol OR LDL OR HDL OR triglyceride OR triglycerides OR low density lipoprotein OR high density lipoprotein OR low-density lipoprotein OR high-density lipoprotein OR HIV OR hiv-1 OR hiv-2* OR hiv1 OR hiv2 OR hiv infect* OR "human immunodeficiency virus" OR "human immune deficiency virus" OR "human immuno-deficiency virus" OR "human immune-deficiency virus" OR "acquired immunodeficiency syndromes" OR "acquired immune deficiency syndrome" OR "acquired immuno-deficiency syndrome" OR "acquired immune-deficiency syndrome" OR HIV/AIDS OR tuberculosis OR tuberculoses OR tb OR "noncommunicable disease" OR "noncommunicable diseases" OR "non-communicable disease" OR "non-communicable diseases" OR NCD OR NCDs OR comorbid* OR co-morbid* OR "co morbidity" OR multimorbidity OR multi-morbid OR "multi morbidity" OR multi-disease* OR multidisease* OR multi disease* OR multiple condition* OR multi-condition* OR multi condition* OR multiple illness* OR multi-illness* OR multi illness* OR multiple syndrome* OR multi-syndrome* OR multi syndrome* OR concurrent condition* OR concurrent illness* OR concurrent disease* OR co-existing disease* OR coexisting disease* OR co-existing illness* OR coexisting illness* OR co-existing syndrome* OR coexisting syndrome* OR co-existing condition* OR coexisting condition* OR co-occurring disease* OR co occuring disease* OR cooccuring disease* OR co-

occurring illness* OR co occurring illness* OR cooccurring illness* OR co-occurring syndrome* OR co occurring syndrome* OR cooccurring syndrome* OR co-occurring condition* OR co occurring condition* OR cooccurring condition* OR chronic disease* OR lifestyle disease* OR "diseases of lifestyle" OR "disease of lifestyle" OR "Multiple Chronic Conditions") AND TOPIC: (“delivery of care” OR “delivery of health” OR "delivery of healthcare" OR "Comprehensive Health Care" OR "comprehensive healthcare" OR "comprehensive care" OR "comprehensive health" OR "Continuity of Patient Care" OR "continuity of patient care" OR "continuity of care" OR "continuity of health" OR "continuity of healthcare" OR "Patient-Centered Care" OR "patient centered care" OR "patient centred care" OR "Referral and Consultation" OR integrat* care OR "integration of care" OR integrat* services OR "integration of services" OR integrat* programmes OR integrat* programs OR “integration of programmes” OR “integration of programs” OR integrat* service delivery OR “integration of service delivery” OR integrat* services OR “integration of services” OR integrat* delivery OR integrat* management OR “integration of management” OR coordinat* care OR "coordination of care" OR coordinat* services OR "coordination of services" OR coordinat* programmes OR coordinat* programs OR “coordination of programmes” OR “coordination of programs” OR coordinat* service delivery OR “coordination of service delivery” OR coordinat* services OR “coordination of services” OR coordinat* delivery OR coordinat* management OR “coordination of management” OR co-ordinat* care OR "co-ordination of care" OR co-ordinat* services OR "co-ordination of services" OR co-ordinat* programmes OR co-ordinat* programs OR “co-ordination of programmes” OR “co-ordination of programs” OR co-ordinat* service delivery OR “co-ordination of service delivery” OR co-ordinat* services OR “co-ordination of services” OR co-ordinat* delivery OR co-ordinat* management OR “co-ordination of management” OR horizontal care OR vertical care OR horizontal services OR vertical services OR horizontal programmes OR horizontal programs OR vertical programmes OR vertical programs OR horizontal service delivery OR vertical service delivery OR horizontal services OR vertical services OR horizontal delivery OR vertical management OR vertical management OR “multi team” OR multiteam “multi care” OR multicare OR “multi clinic” OR multiclinic OR “multi service” OR multiservice OR “multi program” OR multiprogram OR “multi programme” OR “multi delivery” OR multidelivery OR “multi management”) AND TOPIC: (Afghanistan or Albania or Algeria or Angola or Antigua or Barbuda or Argentina or Armenia or Armenian or Aruba or Azerbaijan or Bahrain or Bangladesh or Barbados or Benin or Byelarus or Byelorussian or Belarus or Belorussian or Belorussia or Belize or Bhutan or Bolivia or Bosnia or Herzegovina or Hercegovina or Botswana or Brasil or Brazil or Bulgaria or "Burkina Faso" or "Burkina Fasso" or "Upper Volta" or Burundi or Urundi or Cambodia or "Khmer Republic" or Kampuchea or Cameroon or Cameroons or Cameron or Camerons or "Cape Verde" or "Central African Republic" or Chad or Chile or China or Colombia or Comoros or "Comoro Islands" or Comores or Mayotte or Congo or "Republic of Congo" or Zaire or "Costa Rica" or "Cote d'Ivoire" or "Ivory Coast" or Croatia or Cuba or Cyprus or Czechoslovakia or "Czech Republic" or Slovakia or "Slovak Republic" OR Djibouti or "French Somaliland" or Dominica or "Dominican Republic" or "East Timor" or "East Timur" or "Timor Leste" or Ecuador or Egypt or "United Arab Republic" or "El Salvador" or Eritrea or Estonia or Ethiopia or Fiji or Gabon or "Gabonese Republic" or Gambia or Gaza or Georgia or Georgian or Ghana or "Gold Coast" or Greece or Grenada or Guatemala or Guinea or Guam or Guiana or Guyana or Haiti or Honduras or Hungary or India or Maldives or Indonesia or Iran or Iraq or "Isle of Man" or Jamaica or Jordan or Kazakhstan or Kazakh or Kenya or Kiribati or Korea or Kosovo or Kyrgyzstan or Kirghizia or "Kyrgyz Republic" or Kirghiz or Kirgizstan or "Lao PDR" or Laos or Latvia or Lebanon or Lesotho or Basutoland or Liberia or Libya or Lithuania OR Macedonia or Madagascar or "Malagasy Republic" or Malaysia or Malaya or Malay or Sabah or Sarawak or Malawi or Nyasaland or Mali or Malta or "Marshall Islands" or Mauritania or Mauritius or "Agalega Islands" or Mexico or Micronesia or "Middle East" or Moldova or Moldovia or Moldovian or Mongolia or Montenegro or Morocco or Ifni or Mozambique or Myanmar or Myanma or Burma or Namibia or Nepal or "Netherlands Antilles" or "New Caledonia" or Nicaragua or Niger or Nigeria or "Northern Mariana Islands" or Oman or Muscat

or Pakistan or Palau or Palestine or Panama or Paraguay or Peru or Philippines or Philipines or Phillipines or Phillippines or Poland or Portugal or "Puerto Rico" OR Romania or Rumania or Roumania or Russia or Russian or Rwanda or Ruanda or "Saint Kitts" or "St Kitts" or Nevis or "Saint Lucia" or "St Lucia" or "Saint Vincent" or "St Vincent" or Grenadines or Samoa or "Samoan Islands" or "Navigator Island" or "Navigator Islands" or "Sao Tome" or "Saudi Arabia" or Senegal or Serbia or Montenegro or Seychelles or "Sierra Leone" or Slovenia or "Sri Lanka" or Ceylon or "Solomon Islands" or Somalia or Sudan or South-Sudan or Suriname or Surinam or Swaziland or Syria or Tajikistan or Tadzhikistan or Tadjikistan or Tadzhik or Tanzania or Thailand or Togo or "Togolese Republic" or Tonga or Trinidad or Tobago or Tunisia or Turkey or Turkmenistan or Turkmen or Uganda or Ukraine or Uruguay or USSR or "Soviet Union" or "Union of Soviet Socialist Republics" or Uzbekistan or Uzbek or Vanuatu or "New Hebrides" or Venezuela or Vietnam or "Viet Nam" or "West Bank" or Yemen or Yugoslavia or Zambia or Zimbabwe or Rhodesia OR "developing country" OR "gross domestic" OR "gross national" OR "low income" OR "low-income" OR "middle income" OR "middle-income" OR LMIC OR LMICs OR "transitional country" OR "transitional countries" OR "third world" OR "lami country" OR "lami countries" OR "under developed" OR underdeveloped OR under-developed)

5. CINAHL

S1 MW hypertension OR ((hypertension OR hypertention OR "blood pressure" OR “arterial pressure” OR systolic OR diastolic)) OR ((diabetes OR "diabetes mellitus")) OR MW "Diabetes Mellitus" [320,859]

S2 ((dyslipidaemia OR dyslipidemia OR cholesterol OR LDL OR HDL OR triglyceride OR triglycerides OR low density lipoprotein OR high density lipoprotein OR low-density lipoprotein OR high-density lipoprotein)) OR MW Dyslipidemias OR MW HIV OR MW HIV infections OR ((HIV OR hiv-1 OR hiv-2* OR hiv1 OR hiv2 OR hiv infect* OR "human immunodeficiency virus" OR "human immune deficiency virus" OR "human immuno-deficiency virus" OR "human immune-deficiency virus" OR "acquired immunodeficiency syndromes" OR "acquired immune deficiency syndrome" OR "acquired immuno-deficiency syndrome" OR "acquired immune-deficiency syndrome" OR HIV/AIDS)) OR ((tuberculosis OR tuberculoses OR tb)) OR MW tuberculosis OR (("noncommunicable disease" OR "noncommunicable diseases" OR "non-communicable disease" OR "non-communicable diseases" OR NCD OR NCDs)) OR MW "noncommunicable diseases" OR ((comorbid* OR co-morbid* OR "co morbidity" OR multimorbidity OR multi-morbid OR "multi morbidity")) OR MW multimorbidity OR MW comorbidity [282,133]

S3 ((multi-disease* OR multidisease* OR multi disease* OR multiple condition* OR multi-condition* OR multi condition* OR multiple illness* OR multi-illness* OR multi illness* OR multiple syndrome* OR multi-syndrome* OR multi syndrome* OR concurrent condition* OR concurrent illness* OR concurrent disease* OR co-existing disease* OR coexisting disease* OR co-existing illness* OR coexisting illness* OR co-existing syndrome* OR coexisting syndrome* OR co-existing condition* OR coexisting condition* OR co-occurring disease* OR co occuring disease* OR cooccuring disease* OR co-occurring illness* OR co occurring illness* OR cooccurring illness* OR co-occurring syndrome* OR co occurring syndrome* OR cooccurring syndrome* OR co-occurring condition* OR co occurring condition* OR cooccurring condition*)) OR ((chronic disease* OR lifestyle disease* OR "diseases of lifestyle" OR "disease of lifestyle")) OR MW "Multiple Chronic Conditions” OR MW "Chronic Disease" [141,677]

S4 S2 OR S3 [399,117]

S5 MW "Delivery of Health Care, Integrated" OR MW "Comprehensive Health Care" OR MW "Continuity of Patient Care" OR MW "Patient-Centered Care" [38488]

S6 ((“delivery of care” OR “delivery of health” OR "delivery of healthcare" OR "comprehensive healthcare" OR "comprehensive care" OR "comprehensive health" OR "continuity of patient care" OR "continuity of care" OR "continuity of health" OR "continuity of healthcare" OR "patient centered care" OR "patient centred care") OR ((referral AND consultation)) OR MW ("Referral and Consultation") OR ((integrat* care OR "integration of care" OR integrat* services OR "integration of services" OR integrat* programmes OR integrat* programs OR “integration of programmes” OR “integration of programs” OR integrat* service delivery OR “integration of service delivery” OR integrat* services OR “integration of services” OR integrat* delivery OR integrat* management OR “integration of management”)) OR ((coordinat* care OR "coordination of care" OR coordinat* services OR "coordination of services" OR coordinat* programmes OR coordinat* programs OR “coordination of programmes” OR “coordination of programs” OR coordinat* service delivery OR “coordination of service delivery” OR coordinat* services OR “coordination of services” OR coordinat* delivery OR coordinat* management OR “coordination of management”)) OR ((co-ordinat* care OR "co-ordination of care" OR co-ordinat* services OR "co-ordination of services" OR co-ordinat* programmes OR co-ordinat* programs OR “co-ordination of programmes” OR “co-ordination of programs” OR co-ordinat* service delivery OR “co-ordination of service delivery” OR co-ordinat* services OR “co-ordination of services” OR co-ordinat* delivery OR co-ordinat* management OR “co-ordination of management”)) OR ((horizontal care OR vertical care OR horizontal services OR vertical services OR horizontal programmes OR horizontal programs OR vertical programmes OR vertical programs OR horizontal service delivery OR vertical service delivery OR horizontal services OR vertical services OR horizontal delivery OR vertical management OR vertical management)) OR ((“multi team” OR multiteam “multi care” OR multicare OR “multi clinic” OR multiclinic OR “multi service” OR multiservice OR “multi program” OR multiprogram OR “multi programme” OR “multi delivery” OR multidelivery OR “multi management”)) [145,695]

S7 S5 OR S6 [145,695]

S8 “((developing country" OR "gross domestic" OR "gross national" OR "low income" OR "low-income" OR "middle income" OR "middle-income" OR LMIC OR LMICs OR "transitional country" OR "transitional countries" OR "third world" OR "lami country" OR "lami countries" OR "under developed" OR underdeveloped OR under-developed)) OR ("low- and middle-income") OR ("low and middle income")” [32,715]

S9 S1 AND S4 AND S7 AND S8 [71]

S10 PY 2019 [381,913]

S11 PY 2018 [419,274]

S12 S10 OR S11 [801,187]

S13 S9 AND S12 [17]

6. Africa-Wide Information (via EBSCO host)

S1 SM hypertension OR (hypertension OR hypertention OR "blood pressure" OR “arterial pressure” OR systolic OR diastolic)) OR ((diabetes OR "diabetes mellitus") OR SM "Diabetes Mellitus"

S2 (dyslipidaemia OR dyslipidemia OR cholesterol OR LDL OR HDL OR triglyceride OR triglycerides OR low density lipoprotein OR high density lipoprotein OR low-density lipoprotein OR high-density lipoprotein) OR SM Dyslipidemias OR SM HIV OR SM HIV infections OR (HIV OR hiv-1 OR hiv-2* OR hiv1 OR hiv2 OR hiv infect* OR "human immunodeficiency virus" OR "human immune deficiency virus" OR "human immuno-deficiency virus" OR "human immune-deficiency virus" OR "acquired immunodeficiency syndromes" OR "acquired immune deficiency syndrome" OR "acquired immuno-deficiency syndrome" OR "acquired immune-deficiency syndrome" OR HIV/AIDS) OR (tuberculosis OR tuberculoses OR tb) OR SM tuberculosis OR ("noncommunicable disease" OR "noncommunicable diseases" OR "non-communicable disease" OR "non-communicable diseases" OR NCD OR NCDs) OR SM "noncommunicable diseases" OR (comorbid* OR co-morbid* OR "co morbidity" OR multimorbidity OR multi-morbid OR "multi morbidity") OR SM multimorbidity OR SM comorbidity

S3 (multi-disease* OR multidisease* OR multi disease* OR multiple condition* OR multi-condition* OR multi condition* OR multiple illness* OR multi-illness* OR multi illness* OR multiple syndrome* OR multi-syndrome* OR multi syndrome* OR concurrent condition* OR concurrent illness* OR concurrent disease* OR co-existing disease* OR coexisting disease* OR co-existing illness* OR coexisting illness* OR co-existing syndrome* OR coexisting syndrome* OR co-existing condition* OR coexisting condition* OR co-occurring disease* OR co occuring disease* OR cooccuring disease* OR co-occurring illness* OR co occurring illness* OR cooccurring illness* OR co-occurring syndrome* OR co occurring syndrome* OR cooccurring syndrome* OR co-occurring condition* OR co occurring condition* OR cooccurring condition*) OR (chronic disease* OR lifestyle disease* OR "diseases of lifestyle" OR "disease of lifestyle") OR SM "Multiple Chronic Conditions" OR SM "Chronic Disease"

S4 S2 OR S3

S5 AB "Delivery of Health Care, Integrated" OR AB "Comprehensive Health Care" OR AB "Continuity of Patient Care" OR AB "Patient-Centered Care"

S6 ((“delivery of care” OR “delivery of health” OR "delivery of healthcare" OR "comprehensive healthcare" OR "comprehensive care" OR "comprehensive health" OR "continuity of patient care" OR "continuity of care" OR "continuity of health" OR "continuity of healthcare" OR "patient centered care" OR "patient centred care") OR ((referral AND consultation)) OR SM ("Referral and Consultation") OR (integrat* care OR "integration of care" OR integrat* services OR "integration of services" OR integrat* programmes OR integrat* programs OR “integration of programmes” OR “integration of programs” OR integrat* service delivery OR “integration of service delivery” OR integrat* services OR “integration of services” OR integrat* delivery OR integrat* management OR “integration of management”) OR (coordinat* care OR "coordination of care" OR coordinat* services OR "coordination of services" OR coordinat* programmes OR coordinat* programs OR “coordination of programmes” OR “coordination of programs” OR coordinat* service delivery OR “coordination of service delivery” OR coordinat* services OR “coordination of services” OR coordinat* delivery OR coordinat* management OR “coordination of management”) OR (co-ordinat* care OR "co-ordination of care" OR co-ordinat* services OR "co-ordination of services" OR co-ordinat* programmes OR co-ordinat* programs OR “co-ordination of programmes” OR “co-ordination of programs” OR co-ordinat* service delivery OR “co-ordination of service delivery” OR co-ordinat* services OR “co-ordination of services” OR co-ordinat* delivery OR co-ordinat* management OR “co-ordination of management”) OR (horizontal care OR vertical care OR horizontal services OR vertical services OR horizontal programmes OR horizontal programs OR vertical programmes OR vertical programs OR horizontal service delivery OR vertical service delivery OR horizontal services OR vertical services OR horizontal delivery OR vertical management OR vertical management) OR ((“multi team” OR multiteam “multi care” OR multicare OR “multi clinic”

OR multiclinic OR “multi service” OR multiservice OR “multi program” OR multiprogram OR “multi programme” OR “multi delivery” OR multidelivery OR “multi management”)

S7 S5 OR S6

S8 “(developing country" OR "gross domestic" OR "gross national" OR "low income" OR "low-income" OR "middle income" OR "middle-income" OR LMIC OR LMICs OR "transitional country" OR "transitional countries" OR "third world" OR "lami country" OR "lami countries" OR "under developed" OR underdeveloped OR under-developed) OR ("low- and middle-income") OR ("low and middle income")”

S9 S1 AND S4 AND S7 AND S8

7. LILACS

(Words: hypertension OR "high blood pressure" OR systolic OR diastolic OR diabetes) AND

(Words: dyslipidemia OR cholesterol OR HIV OR tuberculosis OR multimorbidity OR comorbidity OR non-communicable disease) AND

(Words: LMIC OR low income OR middle income OR low-income OR middle-income OR developing country OR developing countries)

Supplementary file 2: List of excluded studies and reasons for exclusion

Studies excluded for wrong population	Studies excluded for wrong study design	Studies excluded for wrong intervention
Abrahams-Gessel 2018[1] Adomaviciute 2014[2] Alharbi 2014[3] Miao 2016[4] Myers 2018[5] Rakic 2011[6] Sarrafzadegan 2006[7] Spaak 2017[8]	Ajay 2016[9] Al Asmary 2013[10] Garrib 2018[11] Germe 2017[12] Kwarisiima 2019[13] Li 2013[14] Mahomed 2014[15] Narayanan 2012[16] Nigatu 2012[17] Nyabera 2011[18] Patel 2018[19] Patel 2015[20] Rabkin 2018[21] Samb 2010[22] Sarraf-Zadegan 2003[23] Sushilkumar 2015[24] Tedjokusumo 2003[25] Tiam 2012[26] Wasay 2009[27]	Bachmann 2018[28] Hong 2013[29] Kowalski 2017[30] McKee 2011[31] Mendis 2010[32] Pibernik-Okanovic 2015[33] Saleh 2018[34] Sarrafzadegan 2009[35] Tourkmani 2018[36] Wenxi 2017[37]

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Supplementary file 3: Summary of interventions according to the TIDiER checklist: Integrated models of care

Study ID	Ameh 2017		Rawat 2018*	Havlir 2019	
Intervention groups	**Intervention**	**Control**	**Intervention**	**Intervention**	**Control**
Name of intervention	Integrated chronic disease management (ICDM) model	Standard care in clinics where ICDM model was not piloted	Implementation of national policy to integrate HIV care into all PHC facilities	Integrated care: Baseline HIV and multi-disease testing plus annual testing, universal ART and patient-centered care	Usual care: Baseline HIV and multi-disease testing and national guideline-restricted ART, hypertension and diabetes care as per country standard of care
Aim of the intervention	To improve management of patients with HIV, TB, hypertension, diabetes, COPD, asthma, epilepsy and mental health conditions at PHCs	Not reported	To provide comprehensive HIV care (prevention, diagnosis, treatment initiation and follow-up) at PHC facilities	To remove patient-level barriers and maximise the efficiency of the health system To overcome barriers of universal access to HIV treatment and to be able to reach UNAIDS goals	Not reported
Physical and informational materials used	Not reported	Not reported	Not reported	Treatment guidelines ART tablets SMS reminders	National treatment guidelines
Procedures, activities and processes used in the intervention	Facility reorganisation: designated chronic care area; supply of critical	Not reported	Policy to integrate HIV care into PHC clinics	Community health campaigns (CHCs): Multi-disease testing for HIV, diabetes and	Community health campaigns: Multi-disease testing for HIV, diabetes and hypertension;

	medicines; pre-packaging of medication Clinical management support: use of guidelines to manage chronic diseases (PC101); human resources audit; capacity building; appropriate referral Ward-based outreach teams to ensure individual responsibility and "assisted" self-management Health promotion and population screening		Training of nurses in comprehensive management of HIV: Nurse initiated Management of ART (NIMART) Training of nurses through the Practical Approach to Lung Health in South Africa (PALSA PLUS) Additional staff to strengthen drug delivery systems	hypertension; counselling and clinic appointments for participants with positive tests; HIV positive participants received blood tests (CD4, t-cell count, HIV/RNA levels) and one-time round trip transportation voucher for first clinic visit Home-based testing for participants that did not attend CHTs Linkage to ART: HIV positive participants not on ART received appointments to initiate ART within a maximum of 7 days; clinic staff introduced themselves in person or by mobile phone; participants could contact hotline via phone or text message for questions or support; phone/SMS reminders about clinic visits Patient-centered care for HIV, diabetes, hypertension: 3-month	counselling and clinic appointments for participants with positive tests; HIV positive participants received blood tests (CD4, t-cell count, HIV/RNA levels) and one-time round trip transportation voucher for first clinic visit ART, diabetes and hypertension treatment: provided in accordance with national guidelines

				visit intervals; flexible clinic hours; reduced waiting time at clinics; welcoming staff; ART to all HIV positive participants; if not eligible for ART according to national guidelines, trial provided Truvada; hypertension and diabetes treated according to standard algorithms	
Who provided the intervention	Nurses	Nurses	Nurses	CHCs: Study team in collaboration with the local health units and the Ministry of Health in Uganda and Kenya Patient-centered care: government clinics augmented by trial staff	CHCs: Study team in collaboration with the local health units and the Ministry of Health in Uganda and Kenya Care in clinics: Clinic staff, augmented by additional staff funded by trial to mitigate staff shortages
Modes of delivery	Not reported	Not reported	Practical implementation of policy varied across clinics: Either disease-specific nurses in separate consulting rooms (co-location), or one nurse that provided comprehensive care for	Face-to-face, via telephone or text message	Face-to-face

			all diseases in single consultation room		
Location of the intervention	Primary healthcare facilities	Primary healthcare facilities	Primary healthcare clinics: 37 urban clinics 65 rural clinics 30 clinics from former homeland	CHCs: Under large tents in all communities, or home-based Patient-centered care: At clinics	CHC: Under large tents in all communities, or home-based ART, diabetes, hypertension care: At clinics
When and how much the intervention was delivered	Unstable HIV and hypertension patients: follow-up every month Stable HIV and hypertension patients: follow=up every 2-3 months Routine referral of all patients to doctor: Every 6 months	Not reported	Not reported	CHCs: lasted 2 weeks at baseline, annually and at 3 year endpoint during weekdays, evenings and weekends Clinic visits: 3-month intervals	CHCs: lasted 2 weeks at baseline and at 3 year endpoint during weekdays, evenings and weekends Clinic visits: not reported
Tailoring of the intervention	Not reported	Not reported	Modular structures and pharmacy renovations to address space concerns in some clinics	Not reported	Not reported
Modifications of the intervention	Not reported	Not reported	Not reported	The end point of the trial was reduced from 5 years to 3 years	Control clinics implemented ART guidelines that were specific to Uganda and Kenya; during the trial, the threshold for eligibility for ART in these

					countries expanded from a specific CD4+ T-cell count (ranging from <350 to <500) to universal treatment (regardless of CD4+ T-cell count)
Assessment of intervention adherence/fidelity	Not reported	Not reported	Not reported	Not reported	Not reported
Intervention delivered as planned	Not reported	Not reported	Not reported	Not reported	Not reported

*No control intervention described

HIV human immunodeficiency virus, TB tuberculosis, COPD chronic obstructive pulmonary disease, PHC primary healthcare clinics

Supplementary file 4: Summary of interventions according to the TIDiER checklist: Interventions to promote integrated management of care

Study ID	Fairall 2016		Prabhakaran 2018	
Intervention groups	**Intervention**	**Control**	**Intervention**	**Control**
Name of intervention	Primary Care (PC) 101	Usual care in for non-communicable and communicable diseases: Practical Approach to Lung Health and HIV/AIDS in South Africa (PALSA PLUS)	mWellcare	Enhanced usual care
Aim of the intervention	To provide comprehensive care for all symptoms, including NCDs, HIV, TB, mental health conditions, women's health	To provide a user-friendly management tool that integrates and harmonises disease-specific guidelines and presents them in a simple format, aligned with patient presentation in primary health care settings, expanded nurses' scope of practice and prescribing (not covering all NCDs)	To facilitate integrated management of hypertension, diabetes, comorbid depression, and alcohol and tobacco use	Not reported
Physical and informational materials used	PC 101 guideline: a 101-page clinical management tool in form of a ring-bound, colour illustrated booklet	Latest version (2011/2012) of PALSA PLUS: clinical management tool	mWellcare system: m-Health-based electronic decision-support system that generates recommendations based on patient profile and risk level, used on Android tablet	Nurses received a tablet to collect baseline data (without the mWellcare system) Visible charts on the management of the conditions

	Desk pads with key messages for priority conditions to facilitate booking of follow-up appointments		Visible charts on the management of the conditions Pamphlets containing lifestyle advice	Pamphlets containing lifestyle advice
Procedures, activities and processes used in the intervention	Training of facility trainers Educational outreach sessions by facility trainers Expanded prescribing provisions for nurses Letters and SMS reminders of follow-up visits Financial compensation for patients (voucher for local grocery store) for travel costs and time	Training of facility trainers Educational outreach sessions by facility trainers Financial compensation for patients (voucher for local grocery store) for travel costs and time	Training of physicians on current clinical management guidelines and orientation to mWellcare system Training of nurses in management of hypertension, diabetes, depression, and tobacco and alcohol use Onsite supervision and support SMS reminders of follow-up visits and medication adherence	Training of physicians on clinical management guidelines for hypertension and diabetes Training of NCD nurses in management of hypertension and diabetes mellitus
Who provided the intervention	Training of facility trainers: Experienced adult education practitioner with a background in nursing, family physician who lead the expansion of the clinical management tool Educational outreach sessions: Nurse trainers	Training of facility trainers: not reported Educational outreach sessions: Nurse trainers Care: Nurses	Training: Study authors Care: NCD nurses and physicians	Training: Study authors Care: NCD nurses and physicians

	Care: Nurses			
Modes of delivery	Training and educational outreach sessions: face-to-face Care: Using PC 101 to guide management, details not reported	Training and educational outreach sessions: face-to-face Care: Using PALSA PLUS to guide management, details not reported	All training: face-to-face Care: Patient baseline data entered into mWellcare system which generated a decision support recommendation, lifestyle advice and suggested date for follow-up (printout). The recommendation was reviewed by the physician. Any changes to the recommended plan we captured in the mWellcare system. The nurse provided lifestyle advice and pamphlets	All training: face-to-face Care: According to clinical judgement of physician. Nurses provided and explained pamphlets on lifestyle advice
Location of the intervention	In primary healthcare clinics	In primary healthcare clinics	Community Health Centres	Community Health Centres
When and how much the intervention was delivered	Training of facility trainers: 5-days, in May 2011 and quarterly 1-day workshops Educational outreach sessions: Total of 155 educational outreach sessions, 8 sessions lasting 90 minutes at each of the 19 intervention clinics Care: Stable patients are seen by the nurse every 3-6 months	Educational outreach sessions: 90 minute sessions Follow-up sessions every year Distribution of updated tool every year Care: Stable patients are seen by the nurse every 3-6 months	Training for nurses using the mWellcare system: 3 days Onsite supervision: 2 days Care: follow-up visits according to the recommendation provided by the mWellcare system	Not reported Care: follow-up visits according to the discretion of the physician

Tailoring of the intervention	Not reported	Not reported	Not reported	Not reported
Modifications of the intervention	Unexpected co-intervention by the district department of health: "Chronic Disease Season" (3 month campaign), to improve NCD recognition and care, focusing on diabetes and hypertension, at clinic and community-level. In the community, free screening of blood pressure and glucose levels were offered in public spaces such as shopping centres. People with high values were referred to the clinic. Training of 33 community health workers to provide basic education on diet and lifestyle Facilitated group session to resolve tensions between nurses, doctors and pharmacists related to expanded prescribing provisions	Unexpected co-intervention by the district department of health: "Chronic Disease Season" (3 month campaign), to improve NCD recognition and care, focusing on diabetes and hypertension, at clinic and community-level. In the community, free screening of blood pressure and glucose levels were offered in public spaces such as shopping centres. People with high values were referred to the clinic. Training of 33 community health workers to provide basic education on diet and lifestyle	None reported	None reported
Assessment of intervention adherence/fidelity	Nurse trainers were observed during 5-day workshop and quarterly 1-day workshops Two nurse trainers were interviewed and focus group discussions were held in four	Not reported	Monthly visits to all sites by field coordinators who complete a checklist on: intervention delivery, source documents examination, protocol	Monthly visits to all sites by field coordinators who complete a checklist on: intervention delivery, source documents examination, protocol

	intervention clinics in December 2011		adherence and recording of adverse events Site visits by investigators: to monitor enrolment process, intervention delivery and protocol adherence	adherence and recording of adverse events Site visits by investigators: to monitor enrolment process, intervention delivery and protocol adherence
Intervention delivered as planned	Good uptake of nurse trainers, who completed all outreach sessions, and repeated some sessions to ensure that most staff could attend Due to absenteeism and shifts, not all nurses attended all the outreach sessions. In total, 18 nurses attended a median of six training sessions, five pharmacists and four doctors were trained Some variations in the uptake of the PC 101 tool were observed	By 2011, 70% of nurses working in the relevant districts had received training in PALSA PLUS.	Not reported	Not reported

Supplementary file 5: Risk of bias assessments for included studies

Prabhakaran 2018

Domain	Risk of bias	Support for judgement
Random sequence generation *(selection bias)*	**Low risk**	"An independent biostatistician performed central computer-based randomization of CHCs stratified by states (Haryana and Karnataka) and within each state by the availability of NCD nurses recruited under NPCDCS." "using block randomisation (with a block size of 2)"
Allocation concealment *(selection bias)*	**Low risk**	Unit of allocation was an institution. Allocation performed on all units at the start of the study.
Baseline outcome measurements similar	**Low risk**	Measurement of outcomes was conducted in a standardised way. Outcomes were pre-defined and subjective
Baseline characteristics similar	**Low risk**	The EUC arm had a higher proportion of participants with peripheral vascular disease (4.4% versus 0.3%), self-reported tobacco use (17.5% versus 10.0%) and alcohol use (12.3% versus 7.8%), and higher mean SBP (157.0 mm Hg versus 152.5 mm Hg). Outcome measures adjusted for relevant baseline characteristics.
Incomplete outcome data	**Low risk**	No incomplete outcome data suspected. Number of participants in whom the outcomes were assessed were mentioned in a general manner.
Blinding of participants and personnel *(performance bias)*	**High risk**	**Outcome group: All/** "Given the nature of the cluster-randomized trial design, neither personnel nor participants were blinded to the intervention."
Blinding of outcome assessment *(detection bias)*	**Unclear**	**Outcome group: All/** "Assessments at study end were carried out by independent outcome assessors" "It was difficult to blind independent assessors who carried out the end-of-study evaluations"
Protection against contamination	**Low risk**	**Outcome group: All/** low possibility of contamination across clusters
Selective Outcome reporting	**Low risk**	Data on cost-effectiveness mentioned in protocol but not reported in full report of the study, because primary outcome do not differ substantially, otherwise all primary and secondary outcomes reported
Recruitment bias *(e.g. individuals are recruited to the trial after the clusters have been randomized)*	**Unclear**	Patients were recruited after randomisation. Of eligible participants, n=165 in the intervention group and n=193 in the control group were not enrolled in the trial.
Baseline differences clusters	**Unclear**	Characteristics of cluster not described
Loss of clusters	**Low risk**	No loss of clusters reported
Incorrect analysis	Low **risk**	Adjusted for clustering
Comparability *(with RCTs randomised by individuals)*	**Low risk**	No similar studies randomised by individuals found in our search.

Fairall 2016

Domain	Risk of bias	Support for judgement
Random sequence generation *(selection bias)*	**Low risk**	"Randomisation was completed by the trial statistician using nQuery Advisor after recruitment of clinics, independently of the managers giving permission for the clinics to be included in the trial, and prior to patient recruitment and implementation of the intervention."
Allocation concealment *(selection bias)*	**Low risk**	Unit of allocation was an institution. Allocation performed on all units at the start of the study. "Randomisation was completed by the trial statistician using nQuery Advisor after recruitment of clinics, independently of the managers giving permission for the clinics to be included in the trial, and prior to patient recruitment and implementation of the intervention"
Baseline outcome measurements similar	**Low risk**	No differences between groups reported: Baseline BP and HbA1C similar
Baseline characteristics similar	**Unclear**	Baseline characteristics seem similar, but no statistical tests reported
Incomplete outcome data	**Low risk**	Loss to follow-up similar across groups and less than 20%
Blinding of participants and personnel *(performance bias)*	**High risk**	**Outcome group: All** **"Blinding of the intervention was not possible at the clinic level due to the nature of the intervention"**
Blinding of outcome assessment *(detection bias)*	**Unclear**	**Outcome group: All** No blinding of outcome assessors reported Outcome assessors not blinded. This might have influenced BP readings, but not HbA1C (blood test)
Protection against contamination	**Unclear**	**Outcome group: All** Contamination of study arms unlikely. Control clinics might have had access to the guidelines although cluster randomisation took place
Selective Outcome reporting	**Low risk**	**No selective outcome reporting suspected, all** outcomes **listed in the methods section are also** reported **in the results section** – All pre-specified outcomes listed in the trial registration record reported on
Recruitment bias	**Low risk**	"Randomisation was completed by the trial statistician using nQuery Advisor after recruitment of clinics, independently of the managers giving permission for the clinics to be included in the trial, and prior to patient recruitment and implementation of the intervention" All patients were enrolled after the clusters were randomised. However, all eligible patients were included in the study.
Baseline differences (clusters)	**Low risk**	Control clinics had more nurses per clinic and more pharmacies on site compared to the intervention group, but patient load was also higher in the control clinics. Ratio of nurses to patients was similar in both groups
Loss of clusters	**Low risk**	All clinics completed the trial
Incorrect analysis	**Low risk**	Analysis conducted on individual level, but results adjusted for cluster effects. "The cluster randomisation design was accounted for using robust cluster variance-covariance estimates."
Compatibility *(with RCTs randomised by individuals)*	**Low risk**	No similar studies randomised by individuals found in our search
Other bias	**Unclear**	"Midway through the trial, the district health department launched a 3-mo campaign called Chronic Disease Season in all clinics to improve NCD recognition and care. Chronic Disease Season focused on hypertension and diabetes and involved both community and clinic health workers. The community-level interventions included several [a]health screening days[o] in which free blood pressure and finger-prick glucose measurements were offered at venues such as shopping centres and town halls" (Page 7, end)

Havlir 2019

Domain	Risk of bias	Support for judgement
Random sequence generation (selection bias)	**Low risk**	Adequate method – mix of methods used, including computer generated, coin tossing and drawing of lots See description in protocol (p45 version 2.0 (Nov 2012)
Allocation concealment (selection bias)	**Low risk**	Communities were matched and randomised within each pair. Method adequate to not be able to predict allocation
Baseline outcome measurements similar	**Unclear**	No baseline outcome measurements for HIV and hypertension control Page 25, online supplement to article
Baseline characteristics similar	**Low risk**	No obvious difference observed
Incomplete outcome data	**Unclear**	Unclear for HIV and Hypertension cohort, not clear how many at baseline.
Blinding of participants and personnel (performance bias)	**High risk**	No blinding of participants and personnel due to the nature of the intervention. Can influence behaviour of both participants and personnel
Blinding of outcome assessment (detection bias)	**Unclear**	Not reported
Protection against contamination	**Unclear**	Distance from other potential trial communities taken into consideration as part of the eligibility criteria. Migration in and out of communities
Selective Outcome reporting	**Unclear**	Not clear whether dual control of HIV and Hypertension/NCDS was pre-specified
Recruitment bias	**Low risk**	Communities were recruited (selected) before randomisation. Participants were recruited after randomisation, but a household census and Community health campaigns to reach most people in community
Baseline differences (clusters)	**Unclear**	No description of clusters, but cluster pairs were matched for randomisation
Loss of clusters	**Low risk**	No loss of clusters
Incorrect analysis	**Unclear**	Not clear whether adequately adjusted for clustering
Compatibility (with RCTs randomised by individuals)	**Low risk**	No similar studies using individual randomisation found in our search
Other bias	**Unclear**	Primary endpoint should have been 5-year cumulative HIV incidence, but this was shortened to 3 years as the WHO recommendation on ART therapy changed

Rawat 2018

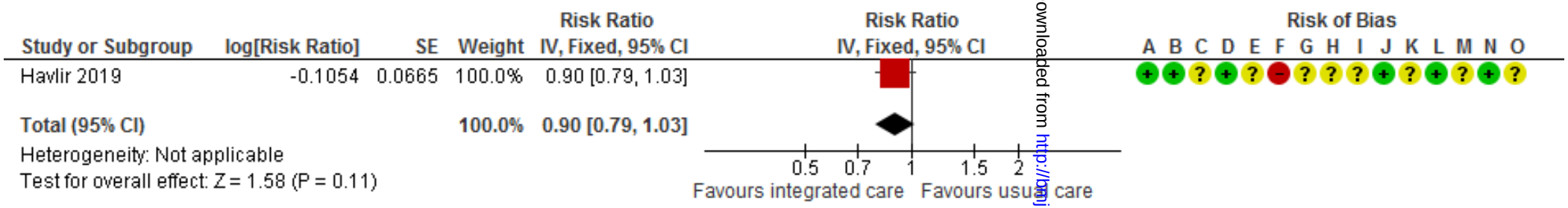
Domain	Risk of bias	Support for judgement
Intervention was independent of other changes	**Low risk**	No other intervention identified. Also, clinics were excluded if they were identified as 'priority sites' that were specifically designed to deliver ART.
The shape of the intervention effect was pre-specified	**High risk**	The shape of the intervention effect was not pre-specified.
The intervention was unlikely to affect data collections	**Low risk**	Data was collected from TIER.net (3 interlinked electronic registers) and the District Health Information System (DHIS) for data collected before and after the intervention.
Knowledge of the allocated intervention *(adequately prevented during the study)*	**Low risk**	Outcomes were based on indicators monitored by the Free State Department of Health. Methods of data collection were similar before and after the intervention, therefore the intervention did not affect data collection.
Incomplete outcome data was likely to bias results	**Unclear**	Post-intervention data for diabetes outcomes only available for 18 months post intervention. For other outcomes there is data for 30 months.
Outcomes were reported selectively	**Low risk**	All outcomes reported in the methods section were reported in the results section
Other risks of bias	**Low risk**	No other risks of bias identified. As integration took place at various intervals, seasonality assumed not to have an effect.

Ameh 2017

Domain	Risk of bias	Support for judgement
Intervention was independent of other changes	**Low risk**	No other changes reported.
The shape of the intervention effect was pre-specified	**Low risk**	Point of analysis is the point of intervention
The intervention was unlikely to affect data collections	**Unclear**	It can be assumed that the re-organisation of care delivery also affected data collection in the intervention facilities
Knowledge of the allocated intervention *(adequately prevented during the study)*	**Low risk**	Data was collected retrospectively from patient records. Patients were recruited in June 2013, and data collected from Jan 2011 to June 2013. Methods of data collection were similar before and after the intervention and the intervention did not affect data collection.
Incomplete outcome data was likely to bias results	**Low risk**	No incomplete outcome data suspected. No attrition or missing cases reported, only data for diabetes patients was not reported because there were too few cases (n=4)
Outcomes were reported selectively	**Low risk**	No selective outcome reporting suspected. All outcomes reported in the methods section are reported in the results section
Other risk of bias	**Low risk**	No other sources of bias identified

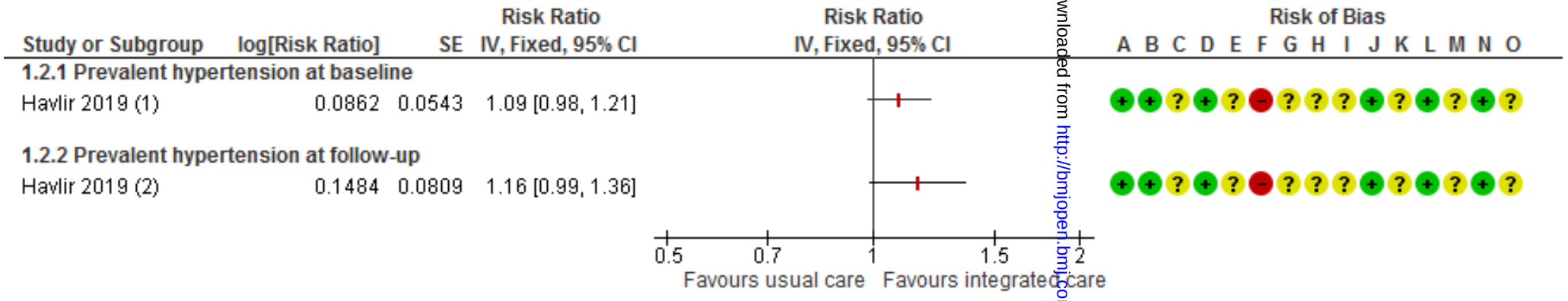
Supplementary file 6: Forest plots

Comparison 1: Integrated models of care vs. usual care
Outcome: Mortality



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Baseline outcome measurements similar
(D) Baseline characteristics similar
(E) Incomplete outcome data (attrition bias)
(F) Blinding of participants and personnel (performance bias)
(G) Blinding of outcome assessment (detection bias)
(H) Protection against contamination
(I) Selective reporting (reporting bias)
(J) Recruitment bias
(K) Baseline differences (clusters)
(L) Loss of clusters
(M) Incorrect analysis
(N) Compatibility with RCTs randomised by individuals
(O) Other bias

Comparison 1: Integrated models of care vs. usual care
Outcome: BP control



Footnotes

(1) Among people living with HIV (PLHIV)

(2) Among people living with HIV (PLHIV)

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Baseline outcome measurements similar

(D) Baseline characteristics similar

(E) Incomplete outcome data (attrition bias)

(F) Blinding of participants and personnel (performance bias)

(G) Blinding of outcome assessment (detection bias)

(H) Protection against contamination

(I) Selective reporting (reporting bias)

(J) Recruitment bias

(K) Baseline differences (clusters)

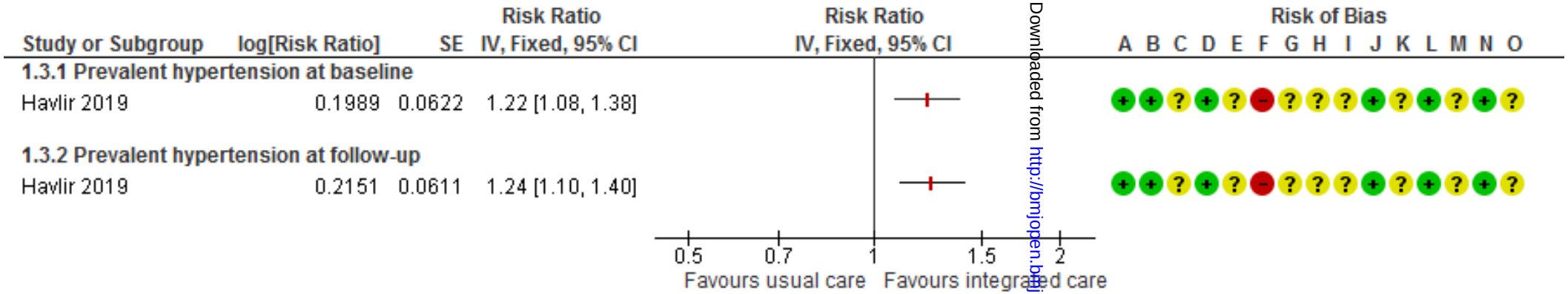
(L) Loss of clusters

(M) Incorrect analysis

(N) Compatibility with RCTs randomised by individuals

(O) Other bias

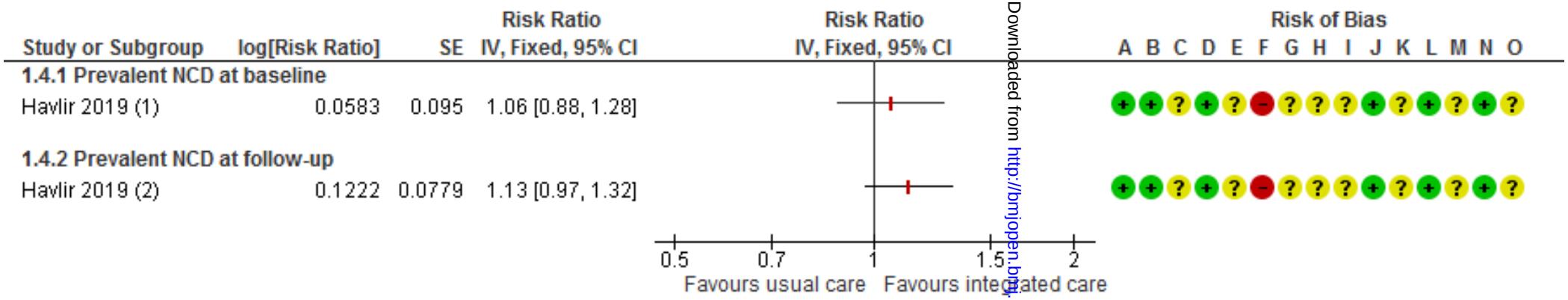
Comparison 1: Integrated models of care vs. usual care
Outcome: BP and HIV control



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Baseline outcome measurements similar
(D) Baseline characteristics similar
(E) Incomplete outcome data (attrition bias)
(F) Blinding of participants and personnel (performance bias)
(G) Blinding of outcome assessment (detection bias)
(H) Protection against contamination
(I) Selective reporting (reporting bias)
(J) Recruitment bias
(K) Baseline differences (clusters)
(L) Loss of clusters
(M) Incorrect analysis
(N) Compatibility with RCTs randomised by individuals
(O) Other bias

Comparison 1: Integrated models of care vs. usual care
Outcome: NCD control



Footnotes
(1) Among PLHIV
(2) Among PLHIV

Risk of bias legend
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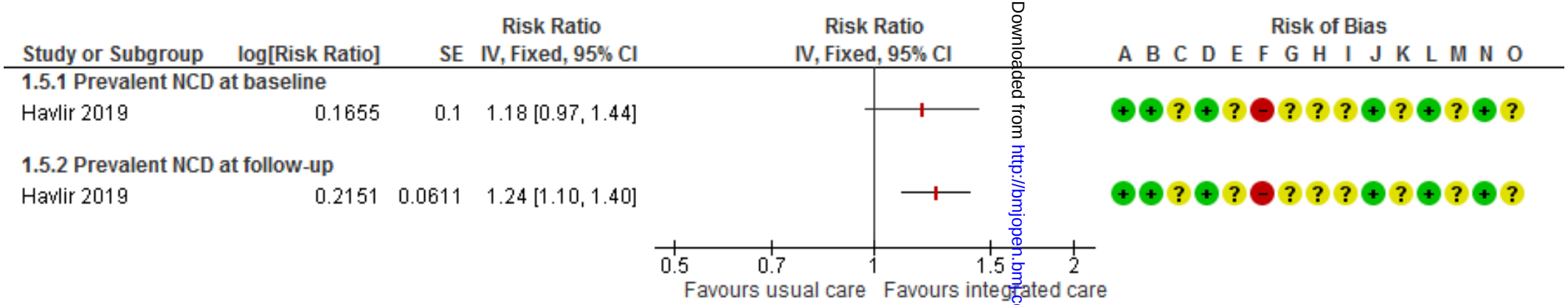
(B) Allocation concealment (selection bias)
(C) Baseline outcome measurements similar
(D) Baseline characteristics similar
(E) Incomplete outcome data (attrition bias)
(F) Blinding of participants and personnel (performance bias)
(G) Blinding of outcome assessment (detection bias)
(H) Protection against contamination
(I) Selective reporting (reporting bias)
(J) Recruitment bias
(K) Baseline differences (clusters)
(L) Loss of clusters
(M) Incorrect analysis
(N) Compatibility with RCTs randomised by individuals
(O) Other bias

Comparison 1: Integrated models of care vs. usual care
Outcome: NCD and HIV control



Risk of bias legend
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(B) Allocation concealment (selection bias)
(C) Baseline outcome measurements similar
(D) Baseline characteristics similar
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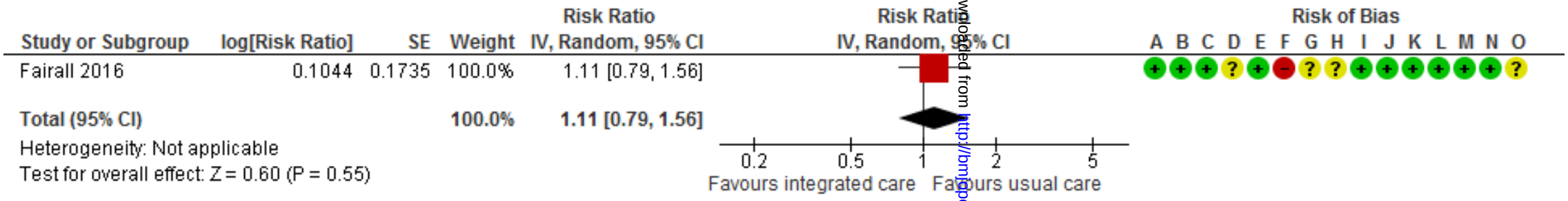
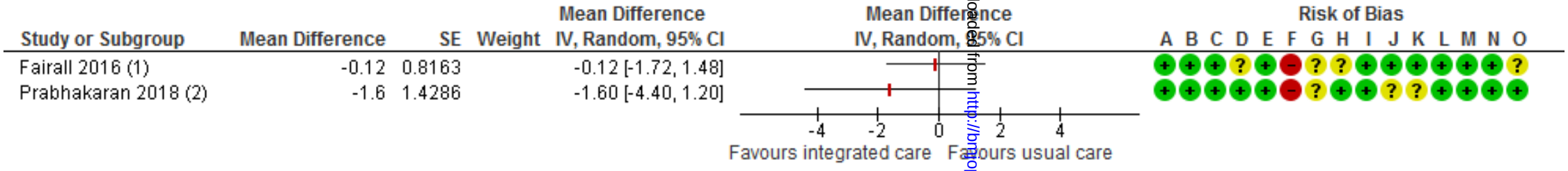
(F) Blinding of participants and personnel (performance bias)
(G) Blinding of outcome assessment (detection bias)
(H) Protection against contamination
(I) Selective reporting (reporting bias)
(J) Recruitment bias
(K) Baseline differences (clusters)
(L) Loss of clusters
(M) Incorrect analysis
(N) Compatibility with RCTs randomised by individuals
(O) Other bias

Comparison 2: Strategies to promote integrated models of care vs. usual care
Outcome: Mortality



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Baseline outcome measurements similar
(D) Baseline characteristics similar
(E) Incomplete outcome data (attrition bias)
(F) Blinding of participants and personnel (performance bias)
(G) Blinding of outcome assessment (detection bias)
(H) Protection against contamination
(I) Selective reporting (reporting bias)
(J) Recruitment bias
(K) Baseline differences (clusters)
(L) Loss of clusters
(M) Incorrect analysis
(N) Compatibility with RCTs randomised by individuals
(O) Other bias

Comparison 2: Strategies to promote integrated models of care vs. usual care
Outcome: Depression



Footnotes

(1) Change from baseline to follow-up; 10-item Center for EpidemiologicStudies...

(2) Value at follow-up; Patient Health Questionnaire-9

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Baseline outcome measurements similar

(D) Baseline characteristics similar

(E) Incomplete outcome data (attrition bias)

(F) Blinding of participants and personnel (performance bias)

(G) Blinding of outcome assessment (detection bias)

(H) Protection against contamination

(I) Selective reporting (reporting bias)

(J) Recruitment bias

(K) Baseline differences (clusters)

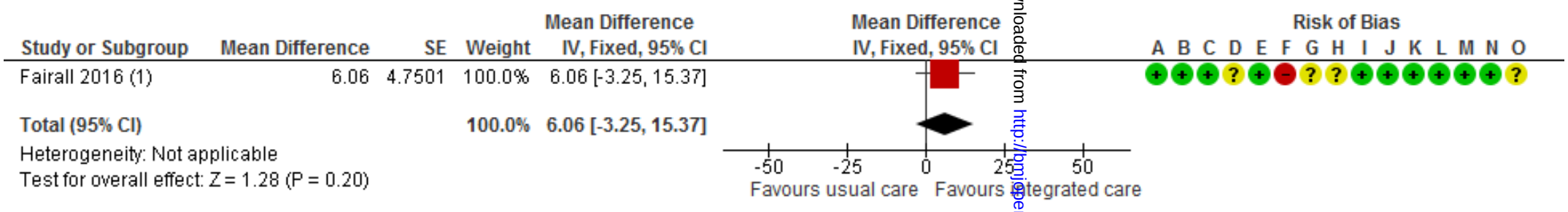
(L) Loss of clusters

(M) Incorrect analysis

(N) Compatibility with RCT of randomised by individuals

(O) Other bias

Comparison 2: Strategies to promote integrated models of care vs. usual care
Outcome: Quality of life



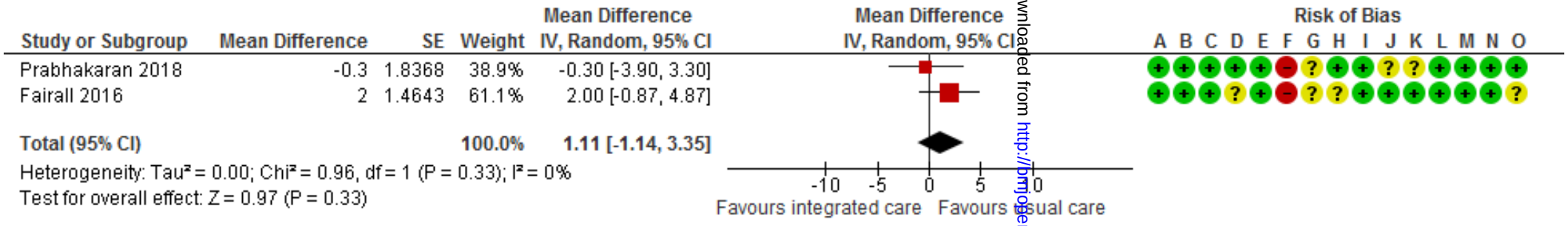
Footnotes

(1) Euro-Qol-5D visual analogue scale: 0=worst imaginable state of health,...

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Baseline outcome measurements similar
(D) Baseline characteristics similar
(E) Incomplete outcome data (attrition bias)
(F) Blinding of participants and personnel (performance bias)
(G) Blinding of outcome assessment (detection bias)
(H) Protection against contamination
(I) Selective reporting (reporting bias)
(J) Recruitment bias
(K) Baseline differences (clusters)
(L) Loss of clusters
(M) Incorrect analysis
(N) Compatibility with RCTs randomised by individuals
(O) Other bias

Comparison 2: Strategies to promote integrated models of care vs. usual care
Outcome: Change in systolic BP



Risk of bias legend
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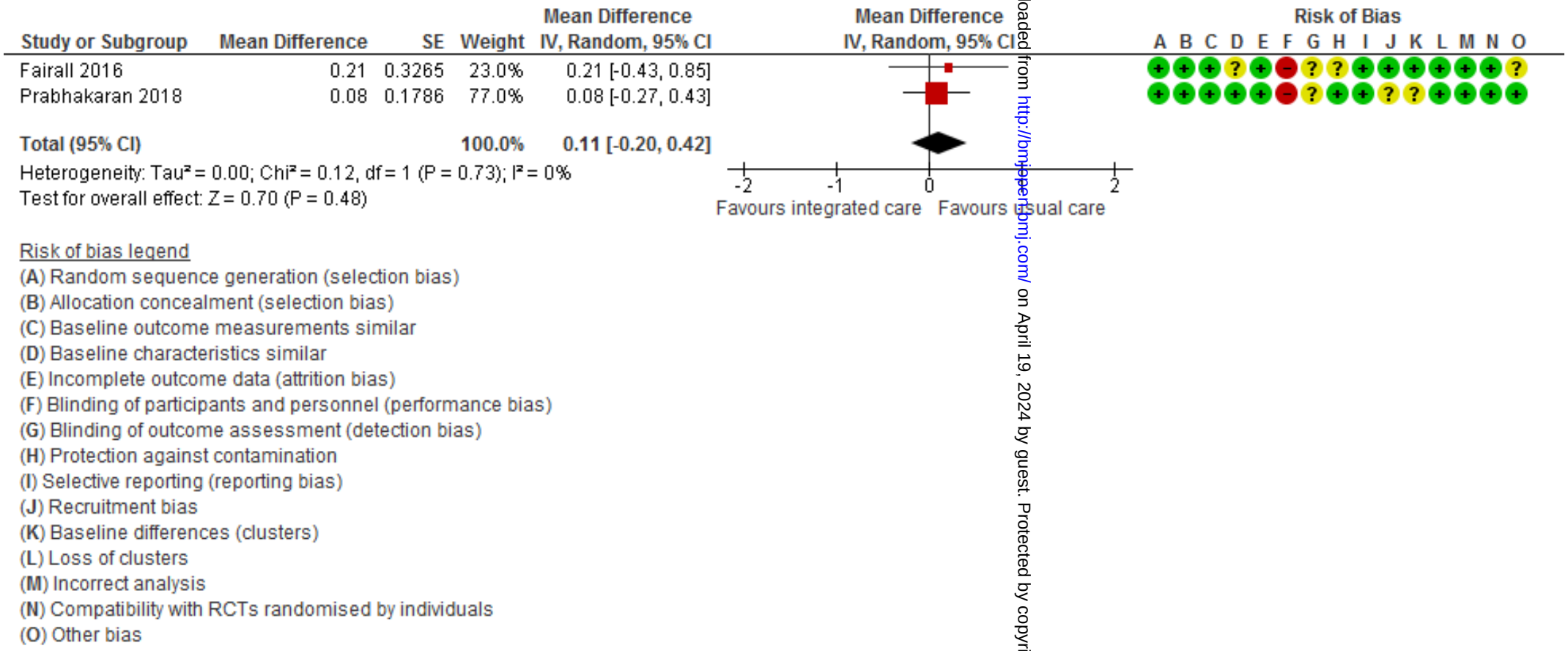
(I) Selective reporting (reporting bias)
(J) Recruitment bias
(K) Baseline differences (clusters)
(L) Loss of clusters
(M) Incorrect analysis
(N) Compatibility with RCTs randomised by individuals
(O) Other bias

Comparison 2: Strategies to promote integrated models of care vs. usual care
Outcome: Change in HbA1c



Risk of bias legend
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(C) Baseline outcome measurements similar
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(F) Blinding of participants and personnel (performance bias)
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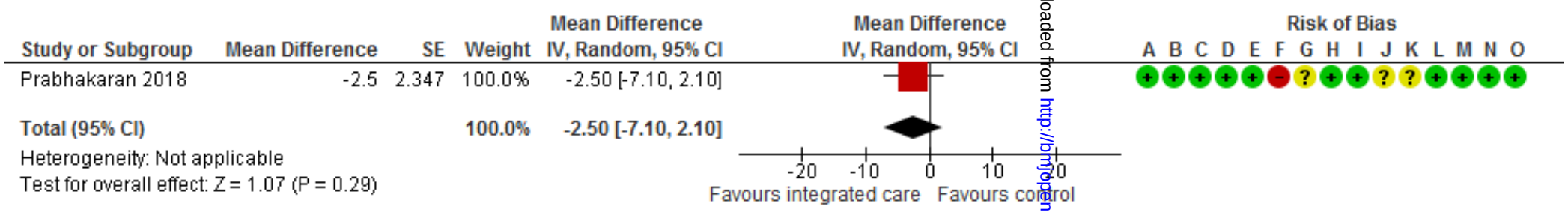
(H) Protection against contamination
(I) Selective reporting (reporting bias)
(J) Recruitment bias
(K) Baseline differences (clusters)
(L) Loss of clusters
(M) Incorrect analysis
(N) Compatibility with RCTs randomised by individuals
(O) Other bias

Comparison 2: Strategies to promote integrated models of care vs. usual care
Outcome: Change in total cholesterol



Risk of bias legend
(A) Random sequence generation (selection bias)
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(C) Baseline outcome measurements similar
(D) Baseline characteristics similar
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(K) Baseline differences (clusters)
(L) Loss of clusters
(M) Incorrect analysis
(N) Compatibility with RCTs randomised by individuals
(O) Other bias

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary file 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6-7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7, Figure 2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-12, Supplementary files 3 and 4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13, Figure 3, 4 and supplementary file 5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Supplementary file 6
Synthesis of results	21	13-20	11-18
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 3 and 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	22

PRISMA 2009 Checklist

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

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BMJ Open

Effects of integrated models of care for diabetes and hypertension in low-and middle-income countries. A systematic review and meta-analysis

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Effects of integrated models of care for diabetes and hypertension in low-and middle-income countries. A systematic review and meta-analysis

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Word count

5380

Keywords

Integrated care, diabetes, hypertension, low-and middle-income countries

Abstract

Objectives

To assess the effects of integrated models of care for people with multi-morbidity including at least diabetes or hypertension in low-and middle-income countries on health and process outcomes.

Design

Systematic review

Data sources

We searched MEDLINE, EMBASE, CENTRAL, LILACS, Africa-Wide, CINAHL, and Web of Science up to 12 December 2019.

Eligibility criteria

We included randomised controlled trials (RCTs), non-RCTs, controlled before-after studies and interrupted time series (ITS) studies of people with diabetes and/or hypertension plus any other disease, in LMICs; assessing the effects of integrated care.

Data extraction and synthesis

Two authors independently screened retrieved records; extracted data and assessed risk of bias. We conducted meta-analysis where possible and assessed certainty of evidence using GRADE.

Results

Of 7568 records, we included five studies - two ITS studies and three cluster RCTs. Studies were conducted in South Africa (n=3), Uganda/Kenya (n=1), and India (n=1). Integrated models of care compared to usual care may make little or no difference to mortality (very low certainty), the number of people achieving blood pressure (BP) or diabetes control (very low certainty), and access to care (very low certainty); may increase the number of people who achieve both HIV and BP/diabetes control (very low certainty); and may have a very small effect on achieving HIV control (very low certainty). Interventions to promote integrated delivery of care compared to usual care may make little or no difference to mortality (very low certainty), depression (very low certainty) and quality of life (very low certainty); and may have little or no effect on HbA1c (low certainty), systolic BP (low certainty), and total cholesterol levels (low certainty).

Conclusions

Current evidence on the effects of integrated care on health outcomes is very uncertain. Programmes and policies on integrated care must consider context-specific factors related to health systems and populations.

PROSPERO registration: CRD42018099314

Strengths and limitations of this study

- We included study designs that are able to provide reliable evidence on the effects of integrated models of care on health and process outcomes
- We performed a comprehensive search for published and unpublished studies up to 12 December 2019, with no language restrictions.

- We assessed the certainty of evidence using the GRADE approach taking into consideration study limitations, inconsistency, imprecision, publication bias and indirectness when downgrading the certainty of evidence.
- Our review did not aim to answer questions on aspects linked to implementation of integrated models of care and barriers and facilitators to integrated models of care at individual and health-system level

Introduction

Low- and middle-income countries (LMICs) are facing an increasing burden of non-communicable diseases (NCDs).[1] A recent report of the World Health Organization (WHO) on NCDs indicates that 41 million people succumb to NCDs globally which is the equivalent of 71% of total global deaths. Fifteen million people die prematurely due NCDs every year (between the ages of 30 and 69 years) and 85% of these premature deaths occur in LMICs.[1 2] Furthermore, NCDs are projected to exceed communicable, maternal, perinatal, and nutritional diseases as the most common causes of death by 2030.[3] In LMICs, the vast majority of NCD deaths are caused by cardiovascular diseases (CVDs), mainly due to coronary artery diseases and stroke,[4] diabetes, cancer and chronic respiratory diseases; and they account for 54% of NCD disability adjusted life years.[1 5] Diabetes and hypertension are the major cardiovascular risk factors for target organ damage of brain, heart and kidney.[1]

Currently, it is estimated that 425 million people in LMICs live with diabetes. This number is expected to increase up to 629 million in 2045.[6] According to the International Society of hypertension, around 40% of people over age of 25 years have hypertension worldwide and two thirds of them live in LMICs.[7] Due to the existing high burden of communicable diseases, especially HIV infection, in sub-Saharan Africa and other LMICs, a lot of people are living with multi-morbidity. Because of the progress made with scaling up of anti-retroviral therapy (ART), the life expectancy of people living with HIV (PLHIV) has increased substantially, putting them at risk of NCDs that are common in older people. In addition to the traditional risk factors for NCDs, such as smoking, poor diet and a sedentary lifestyle, PLHIV have an increased risk of NCDs (especially CVD, cervical cancer, depression and diabetes), related to HIV itself and to ART related side effects[8-11] According to a recent systematic review examining the prevalence of NCDs among PLHIV in LMICs,[12] the pooled prevalence estimate of hypertension was 21.2% (95%CI 16.3 to 27.1); while that of depression was 24.4% (95%CI 12.5 to 42.1%). The prevalence of diabetes among PLHIV was reported to be between 1.2 and 18% and authors ascribed the variation in the findings to actual differences in populations, as well as the lack of standardised diagnostic criteria for diabetes.

In LMICs, people with NCDs such as diabetes and hypertension are generally characterised by very poor outcomes due to various other factors such as limited access to reliable healthcare services.[13] The chronic nature of NCDs puts strain on the already scarce resources of healthcare systems and affected individuals in LMICs.[14] Hence there is a need to design effective interventions to address the increasing burden of NCDs such diabetes and hypertension, in particular in complex patients with co-morbidities such as HIV infection and other CVDs. Provision of integrated care has been advocated by researchers and many international bodies such as the WHO as a way of tackling the rising burden of NCDs and strengthening the health systems particularly in LMICs.[15-17] Recent studies from LMICs have assessed integration of HIV/AIDS and tuberculosis (TB) services at primary healthcare (PHC) level, [18-20] which is usually the first point of contact with health services for people living in LMICs. Based on these integrated models of care, we conceptualised integrated care either as partial integration or full integration as illustrated in Figure 1.[21] Fully integrated care is seen as a “one-stop-shop” model whereby a patient receives all necessary care or services under one roof by one or more health-care professionals. In a partially integrated model of care, patients receiving treatment for one disease such

as diabetes receive additional care related to either prevention, diagnosis or treatment of another disease, but do not receive the full package of care [21].

Although integrated models of care have been widely advocated, and various models and programmes have been implemented and described, there is a lack of evidence on the effectiveness of integrated care compared to other models of care in LMICs. We previously conducted a scoping review to assess existing systematic reviews on the effectiveness of integrated models of care in people with diabetes or hypertension and any other comorbid disease. [22] We found five reviews[23-27] that met our inclusion criteria, but only one of these included studies conducted in LMICs. Furthermore, none of the included studies assessed integrated care for diabetes or hypertension and communicable diseases (e.g. HIV). A subsequent systematic review by Haldane and colleagues examined existing programmes of integrated healthcare delivery for diabetes, hypertension or CVDs with HIV/AIDS.[28] However, included studies mostly described existing programmes with no thorough evaluation of the effectiveness of these programmes. A descriptive study from Cambodia looked at the management of HIV/AIDS, diabetes, and hypertension and found that integration of services for these conditions was highly acceptable and led to good health outcomes with improved CD4 count, glycated haemoglobin (HbA1c) and blood pressure levels.[29] Dudley and Garner[30] assessed the effectiveness of strategies to integrate PHC services in LMICs. They included studies that integrated family planning into existing services; nutrition and infectious disease interventions; and sexually transmitted infections (STIs), HIV/AIDS and TB treatment. None of the included studies reported on NCDs.

In light of limited information in existing reviews, we conducted this review to assess the effects of integrated models of care at PHC level for people living in LMICs, with multi-morbidity, of which diabetes or hypertension is one, compared to no integrated care on health and process outcomes.

Methods

Our systematic review followed the methods pre-specified in a published protocol.[21] We followed the PRISMA reporting guideline to report on the findings of our systematic review.

Criteria for considering studies for inclusion

Types of study designs

Randomised controlled trials (RCTs), including cluster RCTs, controlled (non-randomised) clinical trials (CCTs) or cluster non-randomised trials, interrupted time series (ITS) studies with at least three data points before and after the intervention, and controlled before-and-after (CBA) studies were eligible for inclusion. Cluster randomised, cluster non-randomised or CBA studies were only included if there were at least two intervention sites and two control sites.

Types of participants

We included studies with adults and children attending PHC clinics, presenting with diabetes or hypertension, and patients may potentially have had additional chronic diseases (multi-morbidity) in LMICs. We defined LMICs according to the 2016 classification of the World Bank,[31] that defined low-income economies as those with a gross national income (GNI) per capita of $1035 or less, lower middle income economies as those with a GNI per capita of $1006 to $3995, and upper middle economies as those with a GNI per capita of $3956 to $12235.

Types of interventions

Eligible interventions were models of full or partial integration of services at PHC and community level. Full integration of service delivery was defined as models where patients (primarily treated for diabetes, hypertension or any other disease) received the full package of care (prevention, diagnosis

and treatment) for diabetes or hypertension and any other chronic disease at the same point of care by one or more healthcare professionals. Partial integration of services was defined as models where patients treated for diabetes, hypertension, or any other chronic disease received part of the package of care (either prevention, diagnosis, or treatment) for another disease (see Figure 1). Partially integrated models of care therefore refer to a lower level of integration compared to fully integrated models of care. For example, with partially integrated care, patients receiving treatment for hypertension would be tested for HIV and referred for treatment; whereas with fully integrated care, patients receiving treatment for hypertension would be tested and treated for HIV during the same clinic visit.

Included studies did not provide adequate information for us to categorise interventions as fully integrated models of care or partially integrated models of care and we thus categorised interventions as either 1) integrated models of care or 2) interventions that promoted integrated delivery of care. Integrated models of care assessed the effect of integration of service delivery i.e. integration of two previously separate models of delivery of care into one model of delivery of care, for example integrating HIV services into general PHC services. We distinguished these interventions from interventions that promoted an integrated approach to providing care in PHC facilities. In these cases, services as such were not integrated, but healthcare workers were encouraged to provide holistic patient care, for example through the provision and use of clinical management tools that supported an integrated approach to care.

Types of comparisons

We aimed to compare fully integrated models of care to stand-alone care; partially integrated models of care to stand-alone care; and fully integrated models of care to partially integrated models of care. However, for all included studies, comparisons were reported as standard or usual care and authors did not provide an adequate description of what that entailed. Although these seemed to refer to less integrated care, we unable to categorise them as partially integrated models of care or stand-alone care. We therefore compared integrated models of care to usual care, and interventions to promote integrated delivery of care to usual care.

Types of outcomes

We included studies that reported on either primary or secondary outcomes, as defined by primary study authors. Primary outcomes were all-cause mortality, disease specific morbidity as reported in included studies (e.g. disease control metrics), quality of life, glycated haemoglobin (HbA1c), systolic Blood pressure (SBP) and cholesterol levels. Secondary outcomes were access to care, retention in care, adherence, continuity of care, quality of care and cost of care.

Search strategy

We searched MEDLINE (PubMed), EMBASE (Ovid), the Cochrane Central Register of Controlled Trials (CENTRAL), LILACS, Africa-Wide Information (via EBSCO host), CINAHL, and Web of Science (Core collection) (Date of last search: 12 December 2019). We searched the WHO International Clinical Trials Registry Platform (ICTRP) and Clinicaltrials.gov for ongoing studies, as well as conference abstracts from the International AIDS Society Online Resource Library, the HIV/AIDS Implementers' Meetings and the NCDs Alliance meetings. Search terms included 'diabetes', 'hypertension', 'comorbidities', 'integrated health care delivery', 'low-and middle-income countries', and their synonyms. The full search strategies for all databases are provided in Supplementary file 1. To supplement the search of electronic databases, we screened reference lists of included studies and reference lists of relevant systematic reviews, and contacted experts in the field and relevant organisations (e.g. NCD Alliance) for unpublished studies. We did not have any restrictions related to language, date of publication or publication status.

Selection of studies

Two authors (JUN and AR or a research assistant) independently screened titles and abstracts of studies identified by the search, using Covidence software.[32] We retrieved full texts of potentially eligible studies. Two authors (JUN and AR/TY/CMB) independently screened full texts for eligibility. Discrepancies were resolved through discussion with a third author (JJM/IT). We classified studies as included, excluded or ongoing and provided reasons for excluding studies.

Data extraction

Two authors (JUN, AR and IT) independently extracted data for included studies using a pre-specified, piloted data extraction form and assessed risk of bias. Discrepancies were resolved through discussion or by consulting a third author (TY/JJM). We extracted data related to the study design, participants, intervention, comparison, outcomes, setting, context and funding sources. We used the template for intervention description and replication (TIDieR)[33] and the PRISMA-Complex Interventions extension checklist[34] to guide data extraction and reporting related to the interventions.

Risk of bias assessment

We used guidance from Cochrane Effective Practice and Organisation of Care (EPOC) to assess risk of bias for included studies[35]. Risk of bias was assessed as low, high, or unclear for each domain. For RCTs, non-randomised trials and CBA studies, we assessed the following nine domains: 1) random sequence generation, 2) allocation concealment, 3) baseline outcome measurements, 4) baseline characteristics, 5) incomplete outcome data, 6) knowledge of allocated intervention (blinding), 7) protection against contamination, 8) selective outcome reporting and 9) other risks of bias. For cluster RCTs, we assessed additional risk of bias linked to recruitment, cluster baseline differences, loss of clusters, incorrect analysis and compatibility with RCTs randomised by individuals, as per the Cochrane handbook.[36] For ITS studies, we assessed whether 1) the intervention was independent of other changes, 2) the shape of the intervention effect was pre-specified, 3) the intervention was unlikely to affect data collections, 4) knowledge of the allocated intervention was adequately prevented during the study, 5) incomplete outcome data was likely to bias results, 6) outcomes were reported selectively and 7) there were any other risks of bias.

Data analysis

We extracted relevant data for each outcome per included study. For dichotomous outcomes, we reported risk ratios (RR) and 95% confidence intervals (CI). For continuous outcomes, we reported mean differences (MD) with 95% CI if outcomes were measured in the same way across studies, or standardised mean differences (SMD) with 95% CI where outcomes were measured differently across studies and where standard deviations (SD) were reported. For ITS studies, we reported beta coefficients (β) with 95% CI or standard error (SE). We contacted study authors to request information on missing data. We did not impute any data.

All included cluster RCTs appropriately adjusted for the effects of clustering in their analysis, we thus used these adjusted effect estimates and standard errors in our meta-analysis using the generic inverse-variance method in Review Manager 5.[37] We did not include studies with more than one treatment arm in our review.

We explored clinical heterogeneity by clearly documenting study characteristics related to the population, intervention, outcomes and context in table format. We assessed statistical heterogeneity in each meta-analysis by inspecting forest plots and calculating Chi^2 test values and I^2 statistics. We considered heterogeneity to be important if the p-value of the Chi^2 test was < 0.10, and the I^2 statistic was above 30%, as per the recommendations in the Cochrane handbook.[36]

We pooled data from individual studies if we judged them to be sufficiently homogeneous in terms of design, population, intervention and comparator. As we anticipated some degree of heterogeneity, we performed random-effects meta-analysis. We did not pool data from RCTs and non-randomised studies in a single meta-analysis. Where we judged included studies to be too heterogeneous to pool, we used narrative synthesis and presented data in tabular format. We did not perform subgroup or sensitivity analysis, as only two studies contributed to the meta-analysis. We were unable to examine reporting biases by means of funnel plots, as we only included two studies in the meta-analysis.

Certainty of evidence

We wrote statements about the evidence (e.g., "little or no effect" vs. "very small effect") according to guidance of GRADE[38] for the following outcomes: mortality, disease specific morbidity, quality of life, HbA1c, systolic BP, cholesterol levels and access to care. We created a 'Summary of findings' table using GRADEpro software.[39] Our judgements to downgrade the certainty of evidence were based on assessment of the following five domains: 1) study limitations, 2) inconsistency, 3) imprecision, 4) indirectness and 5) publication bias. According to GRADE guidance, non-randomised studies (such as CBAs and ITS studies) start at low certainty evidence. We considered upgrading the certainty of evidence for non-randomised studies if there was a large effect, a dose-response and cases where all plausible residual confounding would reduce a demonstrated effect or would suggest a spurious effect if no effect was observed.

For each outcome, we described the certainty of evidence as high, moderate, low or very low.[40] For outcomes reported by both RCTs and non-randomised studies, we made separate GRADE judgements for both types of studies. Where we arrived at the same level of certainty of evidence, we summarised this in a single judgement per outcome. We interpreted the certainty of evidence according to guidance provided by the GRADE working group, which takes into consideration the size of the effect and the certainty of evidence.[41]

Patient and public involvement

No patients were involved in the development of this systematic review.

Results

The results of the search are depicted in the PRISMA flow diagram (Figure 2). We screened titles and abstracts of 7568 records. We obtained and screened full texts of 49 potentially relevant studies. We included five studies,[42-46] (Table 1) reported in six articles and excluded 37 articles and reported reasons for exclusion (Supplementary file 2). For one study[47] that met eligibility criteria, we were only able to access the conference abstract. We classified this study as 'awaiting assessment', as we are unable to definitively decide on inclusion or exclusion until we have access to the full report. We identified five ongoing RCTs,[48-51] investigating integrated care for depression and hypertension in China;[48] integrated care for depression and hypertension[49] or depression and diabetes/HIV[50] in South Africa; integrated care for common mental disorders and hypertension, diabetes or ischemic heart disease in India;[51] and diabetes and TB in India.[52]

Table 1: Summary of characteristics of included studies

Study ID	Study design	Country and Setting	Participants	Intervention	Control	Study duration (follow-up)	Outcomes[1]
Integrated models of care							
Ameh 2017[42]	Controlled ITS study	South Africa: Primary health care (PHC) facilities, Ehlanzeni health district, Mpumalanga Province	Patients with chronic disease (HIV, diabetes or hypertension) n=878	Integrated chronic disease management (ICDM) model Clinics: n=7 Participants: n=435 (Hypertension: n=210; Diabetes: n=2; HIV: n=141; Comorbidities: n=82)	Usual care in PHC facilities Clinics: n=5 Participants: n=443 (Hypertension: n=91; Diabetes: n=2; HIV: n=282; Comorbidities: n=68)	30 months Pre-intervention: 6 months Post-intervention: 24 months	- **Blood pressure (BP) control[2]** - **CD4 count control[3]** - **Number of healthcare visits**
Havlir 2019[46]	Cluster RCT	Kenya and Uganda: Rural regions in south-western and eastern Uganda, and western Kenya	Clusters: Communities of 9000 to 11 000 people Participants: People residing in community n=150 395 (baseline)	Integrated care: Baseline HIV and multi-disease testing plus annual testing, universal ART and streamlined, patient-centered care Clusters: n=16 Participants: n=79 818 (baseline) (Hypertension in adults over 30 years: n=5953)	Usual care: Baseline HIV and multi-disease testing and national guideline-restricted ART, hypertension and diabetes care as per country standard of care (not integrated) Clusters: n=16 Participants: n=70 577 (baseline)	36 months	- Cumulative HIV incidence - Time to initiation of ART - Viral suppression - **Death** - Incident tuberculosis or death due to illness - **Control of hypertension[4] among HIV-infected persons** - **Control of diabetes[5] or hypertension (NCD) among HIV infected persons** - **Control of HIV[6] and hypertension** - **Control of HIV and NCDs[7]**

[1] Outcomes relevant to this review are in bold
[2] Defined as: BP <140/90mmHg
[3] Defined as: CD4 count >350 cells/mm^3
[4] Defined as: At least one systolic BP measurement <140mmHg, and at least one diastolic measurement of <90mmHg
[5] Defined as: Finger prick blood glucose ≤11 mmol/L
[6] Defined as: Suppressed viral replication (<500 copies/ml)
[7] Defined as: Control of all prevalent NCDs (hypertension or diabetes)

					(Hypertension in adults over 30 years: n=5911)		- Control of hypertension in the overall population - Control of diabetes in the overall population
Rawat 2018[45]	ITS study	South Africa: PHC clinics in the Free state Province	Patients attending PHC clinics (focus on diabetes and hypertension) n=not reported	Integration of HIV care into HC facilities n=131 clinics	No control group	48 months Pre-intervention: 12 months Post-intervention: 36 months	- **Population level new diabetics on treatment** - **Clinic level new diabetics on treatment** - **Population-level new hypertensive on treatment** - **Clinic level new hypertensive on treatment** - **Total ART patients** - **New patients initiated on ART**
Interventions to promote integrated delivery of care							
Fairall 2016[43]	Cluster RCT	South Africa: Mostly rural PHC clinics in Eden and Overberg districts, Western Cape Province	Patients with one or more of the following: hypertension, diabetes, chronic respiratory disease, depression n=4393	Primary Care (PC) 101 management tool Clinics: n=19 Participants: n=2166 (Hypertension: n=1555; diabetes: n=851)	Usual care: Practical Approach to Lung Health and HIV/AIDS in South Africa (PALSA PLUS) management tool Clinics: n=19 Participants: n=2227 (Hypertension: n=1672; diabetes: n=991)	14 months	- Treatment intensification for hypertension, diabetes and chronic respiratory disease - **Depression** - CVD risk - **Systolic BP** - **HbA1C** - Body Mass Index (BMI) - Smoking status - **Health-related quality of life** - **Mortality** - **Healthcare utilisation**
Prabhakaran 2019[44]	Cluster RCT	India: Community Health Centres (CHC) from 4 districts in Haryana and 2 districts in Karnataka	Patients with confirmed diagnosis of diabetes or hypertension n=3698	mWellcare system CHCs: n=20 Participants: n=1842	Enhanced usual care CHCs: n=20 Participants: n=1856	12 months	- **Mean change in systolic BP** - **Mean change in HbA1C** - Mean change in fasting plasma glucose - **Mean change in total cholesterol** - Mean change in CVD risk - Mean change in Tobacco use - Mean change in BMI - Alcohol use

							- **Depression score** - **Adherence** - **Perceived quality of care**

Characteristics of included studies

We included three cluster RCTs and two ITS studies. One cluster RCT was conducted in South Africa,[43] one in India,[44] and the Sustainable East Africa Research in Community Health (SEARCH) trial was conducted in Uganda and Kenya.[46] The two ITS studies were both conducted in South Africa[42 45] (Table 1). All studies were conducted in PHC facilities in mostly rural settings. All five studies assessed the effect of strategies for full integration of care compared to partial integration of care.

The two ITS studies[42 45] and the SEARCH trial[46] assessed the effects of integrated models of care for chronic diseases (Table 2). Ameh and colleagues[42] conducted a controlled ITS study, comparing the integrated chronic disease management (ICDM) model to usual care over a period of 30 months. Rawat and colleagues[45] examined the effect of integrating HIV care into PHC clinics over a 48 months period. The SEARCH trial[46] assessed the effects of universal ART and streamlined, patient-centered care (integrated care) compared to usual care as per national guidelines. Interventions are described in more detail according to the TIDieR checklist in supplementary file 3.

The other two cluster RCTs[43 44] assessed the effectiveness of interventions to promote integration of care (Table 2). Fairall and colleagues[43] introduced the Primary Care (PC) 101 clinical management tool to promote provision of comprehensive care for all symptoms including NCDs, HIV, TB, mental health and women's health, in PHC clinics randomised to the intervention, while the control clinics continued using the Practical Approach to Lung Health and HIV/AIDS in South Africa (PALSA PLUS) management tool, which did not cover all NCDs and was the standard of care at the time of the trial. Prabhakaran and colleagues[44] introduced the mWellcare system, a m-health based electronic decision support system, to promote integrated management of hypertension, diabetes, depression, and alcohol and tobacco use in PHC centres randomised to the intervention. Control centres continued with usual care. Interventions are described in more detail according to the TIDieR checklist in supplementary file 4.

Table 2: Key components of included interventions

Name and Study ID	**Components related to provision of care in the clinic**	**Components related to provision of care in the community/at home**	**Training**	**Appointment reminders**
Integrated chronic disease management (ICDM) model Ameh 2017	Facility reorganisation: designated chronic care area; supply of critical medicines; pre-packaging of medication Clinical management support: use of guidelines to manage chronic diseases (PC101); human resources audit; capacity building; appropriate referral	Ward-based outreach teams to ensure individual responsibility and "assisted" self-management Health promotion and population screening	-	-

National policy to integrate HIV care into all PHC facilities Rawat 2018	Policy to integrate HIV care into PHC clinics Either disease-specific nurses in separate consulting rooms (co-location), or one nurse that provided comprehensive care for all diseases in single consultation room Additional staff to strengthen drug delivery systems	-	Training of nurses in comprehensive management of HIV: Nurse initiated Management of ART (NIMART) Training of nurses through the Practical Approach to Lung Health in South Africa (PALSA PLUS)	-
SEARCH intervention Havlir 2019	Patient-centered, integrated care for HIV, diabetes, hypertension: 3-month visit intervals; ART to all HIV positive participants; hypertension and diabetes treated according to standard algorithms	Community health campaigns (CHCs): Testing for HIV, diabetes and hypertension; counselling and clinic appointments; blood tests for HIV positive participants; transportation voucher for first clinic visit Home-based testing for participants that did not attend CHCs Appointments to initiate ART within 7 days for HIV positive participants not on ART; introductory phone call from clinic staff; support hotline available via phone or text message	-	Phone/SMS reminders about clinic visits
Primary Care (PC) 101 Fairall 2016	PC 101 guideline: Ring-bound, colour illustrated booklet Expanded prescribing provisions for nurses Desk pads with key messages	-	Training of facility trainers Educational outreach sessions by facility trainers	Letters and SMS reminders of follow-up visits

mWellcare Prabhakaran 2018	mWellcare system: m-Health-based electronic decision-support system Visible charts on the management of the conditions Onsite supervision and support	Pamphlets containing lifestyle advice	Training of physicians on current clinical management guidelines and orientation to mWellcare Training of nurses in management of hypertension, diabetes, depression, and tobacco and alcohol use	SMS reminders of follow-up visits and medication adherence

Risk of bias in included studies

For the two ITS studies, we judged risk of bias to be low or unclear in all domains (Figure 3). For the three cluster RCTs, we judged risk of selection bias to be low, risk of performance bias to be high, as blinding of participants and personnel was not possible due to the nature of the interventions, and risk of detection bias to be unclear for all three studies. We judged attrition bias to be low for two cluster RCTs[43 44] and unclear for the SEARCH trial[46] (Figure 4). Detailed judgements for each included study are reported in supplementary file 5.

Integrated models of care compared to usual care

We included three studies as part of this comparison.[42 45 46] Results are summarised in the summary of findings table (Table 3) and forest plots are available in supplementary file 6.

Table 3: Summary of findings for integrated models of care compared to usual care for diabetes and hypertension in LMICs

Patient or population: Patients with multi-morbidity (diabetes and/or hypertension and other chronic conditions e.g. HIV) **Setting**: Low- and middle-income countries **Intervention**: Integrated care for hypertension, diabetes and HIV **Comparison**: Usual care				
Outcome	**Effect (95%CI)**	**No of participants (studies)**	**Certainty of evidence (GRADE)**	**Comments**
Mortality	RR 0.90 (0.79 to 1.02) Risk with usual care: 0.56 per 100 person-years Risk with integrated care: 0.51 per 100 person-years	171 431 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	Integrated care compared to usual care may make little or no difference to the rate of death, but the evidence is very uncertain
BP control (number of PLHIV achieving BP control)	RCT: Prevalent hypertension at baseline: RR 1.09 (0.98 to 1.21) RCT: Prevalent hypertension at follow-up: RR 1.16 (0.99 to 1.36) ITS study: β=0.010 (0.003 to 0.016)	2319 (2 studies: 1 RCT, 1 ITS study)	⊕◯◯◯ VERY LOW [a,c,d,e,f]	Integrated care compared to usual care may make little or no difference to achieving BP control but the evidence is very uncertain
BP or diabetes (NCD) control (number of PLHIV achieving NCD control)	Prevalent NCD at baseline: RR 1.06 (0.88 to 1.27) Prevalent NCD at follow-up: RR 1.13 (0.97 to 1.32)	1 RCT*	⊕◯◯◯ VERY LOW [a,c,d]	Integrated care compared to usual care may make little or no difference to achieving NCD control but the evidence is very uncertain
HIV control (CD4 count control)	The probability of CD4 count control was 6% greater in intervention clinics compared to control clinics	878 (1 ITS study)	⊕◯◯◯ VERY LOW [e,f]	Integrated care may have a very small effect on achieving CD4 count control, but the evidence is very uncertain
BP and HIV control (number of people achieving both HIV viral suppression and BP control)	Prevalent hypertension at baseline: RR 1.22 (1.08 to 1.37) Prevalent hypertension at follow-up: RR 1.24 (1.10 to 1.40)	1441 (1 RCT)	⊕◯◯◯ VERY LOW [a,c,d]	Integrated care compared to usual care may result in a slight increase in the number of people achieving both BP and HIV control but the evidence is very uncertain
BP or diabetes (NCD) and HIV control (number of people achieving both HIV viral suppression and NCD control)	Prevalent NCD at baseline: RR 1.18 (0.97 to 1.44) Prevalent NCD at follow-up: RR 1.24 (1.10 to 1.40)	1441 (1 RCT)	⊕◯◯◯ VERY LOW [a,c,d]	Integrated care compared to usual care may result in a slight increase in the number of people achieving both NCD and HIV control but the evidence is very uncertain
Quality of life	-	-	-	Not reported
Systolic BP	-	-	-	Not reported
HbA1c	-	-	-	Not reported
Cholesterol levels		-	-	Not reported

Access to care	There was no change in trend from pre- to post-intervention for population level new diabetics on treatment, clinic level new diabetics on treatment and clinic-level new hypertensive patients on treatment. There was a slight decrease in new hypertensive patients on treatment at population level at 36 months	1 ITS*	⊕◯◯◯ VERY LOW e,g	Integrated care may make little or no difference to short term access to care and may result in a slight decrease in long-term access to hypertensive care, but the evidence is very uncertain.

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; BP: Blood pressure; HIV: Human Immunodeficiency Virus; HbA1c: Glycated Haemoglobin; NCD: Non-communicable disease; RCT: Randomised controlled Trial; ITS: Interrupted time series

*Sample size not reported

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Footnotes: Explanation of GRADE certainty of evidence

Randomised controlled trials:

a) Downgraded by 1 due to study limitations: high risk of performance bias and unclear risk of bias for other domains

b) Downgraded by 1 due to indirectness: Results are based on number of participants at baseline, however authors did not report how many participants had HIV plus hypertension/diabetes at baseline. At 3-year follow-up, less than 1% of participants at follow-up had hypertension/diabetes and HIV infection (0.7% (694/103 777) in the control group and 0.6% (747/121 347) in the intervention group)

c) Downgraded by 1 due to indirectness: Usual care comprised care according to national guidelines in Kenya and Uganda. Authors did not report what this entails. It is not clear to what extend care was integrated or not

d) Downgraded by 1 due to imprecision: Small sub-sample with hypertension and HIV in the RCT with wide 95% confidence intervals

Interrupted time series studies:

e) Observational study, starting at low certainty evidence

f) Downgraded by 1 due to indirectness: Intervention clinics experienced stock-outs of anti-hypertensive drugs and malfunctioning of BP machines. We are therefore not confident that the intervention was delivered as intended

g) Downgraded by 1 due to indirectness: Study reported on population level new diabetics on treatment, clinic level new diabetics on treatment, population level new hypertensive patients on treatment and clinic level new hypertensive patients on treatment. This is an indirect measure of access to care

All-cause mortality: The SEARCH trial[46] reported the rate of all-cause mortality among baseline residents in included communities. Results suggest that integrated compared to usual care may make little or no difference to the mortality rate when compared to usual care but the evidence is very uncertain (RR 0.90 95%CI 0.79 to 1.02, n=171 431, 1 RCT, very low-certainty evidence).

Disease-specific morbidity (BP control): Integrated care compared to usual care may make little or no difference to achieving BP control, but the evidence is very uncertain. Results from the SEARCH trial[46] suggest that integrated care compared to usual care may make little or no difference to the number of PLHIV who achieve BP control with prevalent hypertension at baseline (RR 1.09, 95%CI 0.98 to 1.21, 1 RCT, very low-certainty evidence) and PLHIV with prevalent hypertension at follow-up (RR 1.16, 95%CI 0.99 to 1.36, n=1441, 1 RCT, very low- certainty evidence). Results of the controlled ITS study[42] suggest that integrated care compared to usual care may increase the probability of achieving BP

control by 1%, but the evidence is very uncertain (β=0.010, 95%CI 0.003 to 0.016, n=878, 1 ITS study, very low-certainty evidence).

Disease-specific morbidity (NCD control): Results from the SEARCH trial [46] suggest that integrated care compared to usual care may make little or no difference to the number of PHLV who achieve NCD (diabetes and/or hypertension) control with prevalent NCD at baseline (RR 1.06, 95%CI 0.88 to 1.27, 1 RCT, very low-certainty evidence) and prevalent NCD at follow-up but the evidence is very uncertain (RR 1.13, 95%CI 0.97 to 1.32, 1 RCT, very low-certainty evidence).

Disease-specific morbidity (HIV control): One ITS study[42] reported on HIV control in terms of CD4 count control. Results suggest that integrated care compared to usual care may increase the probability of achieving CD4 count control by 6%, but the evidence is very uncertain (β=0.057, 95%CI 0.056 to 0.058, n=878, 1 ITS study, very low-certainty evidence).

Disease-specific morbidity (HIV and BP control): Results from the SEARCH trial[46] suggest that integrated care compared to usual care may increase the number of PLHIV who achieve both HIV viral suppression (HIV control) and BP control with prevalent hypertension at baseline (RR 1.22, 95%CI 1.08 to 1.37, 1 RCT, very low-certainty evidence) and with prevalent hypertension at follow-up (RR 1.24, 95%CI 1.10 to 1.40, n=1441, 1 RCT, very low-certainty evidence).

Disease-specific morbidity (HIV and NCD control): Integrated care compared to usual care may make little or no difference to the number of PLHIV who achieve both HIV viral suppression (HIV control) and NCD control with prevalent NCD at baseline (RR 1.18, 95%CI 0.97 to 1.44, 1 RCT, very low certainty), but may result in a slight increase in the number of PLHIV who achieve both HIV viral suppression (HIV control) and NCD control with prevalent NCD at follow-up (RR 1.24, 95%CI 1.10 to 1.40, 1 RCT very low-certainty evidence). However, the evidence is very uncertain for these outcomes.

Access to care: One ITS study reported on access to care[45] in terms of the change in post-integration trend compared to pre-integration trend for population level new diabetics on treatment, clinic level new diabetics on treatment, population-level new hypertensive patients on treatment, and clinic level new hypertensive patients on treatment. Integrated care may make little or no difference to population level new diabetics on treatment at 18 (1/100 000, Standard Error (SE)=2, p=0.50, very low certainty) and 36 months (1/100 000, SE=3, p=0.61, very low-certainty evidence) post-integration; clinic level new diabetics on treatment at 18 (0/100 000, SE=1; p=0.96, very low-certainty evidence) and 36 months post-integration; clinic level new hypertensive patients on treatment at 18 (0/100 000, SE=1; p=0.78, very low-certainty evidence) and 36 months (0/100 000, SE=0; p-value=0.57, very low-certainty evidence) post-integration, and population level new hypertensive patients on treatment at 18 months post-integration (-7/100 000, SE=4; p=0.08, very low-certainty evidence). Results suggest that there was a slight decrease in population level new hypertensive patients on treatment at 36 months post-integration (-6/100 000; SE=3; p=0.02, very low-certainty evidence). However, the evidence is very uncertain for these outcomes.

Authors also reported on the total number of patients on anti-retroviral treatment (ART) and the number of new patients initiated on ART. Overall, the number of patients for both outcomes increased during each year of follow-up. No effect size was reported. No other secondary outcomes were reported for this comparison.

Interventions to promote integrated delivery of care compared to usual care

We included two studies in this comparison.[43] [44] Results are summarised in the summary of findings table (Table 4) and forest plots are available in supplementary file 6.

All-cause mortality: Results from one cluster RCT[43] suggest that interventions to promote integrated care compared to usual care may make little or no difference in mortality (RR 1.11; 95% CI 0.79 to 1.56;

n=3393; 1 RCT, very low-certainty evidence) when compared to usual care, but the evidence is very uncertain.

Disease-specific morbidity (depression): Results from two RCTs[43 44] suggest that interventions to promote integrated care compared to usual care may have little or no effect on change in HbA1c from baseline to follow-up (MD 0.11%; 95%CI -0.20 to 0.42; n=1687; 2 RCTs, low-certainty evidence). This means that the change in HbA1c was similar in both groups. Fairall 2016 reported the change in depression scores from baseline to follow up using the 10-item Center for Epidemiologic Studies Depression Scale and reported no difference between groups (MD −0.12; 95%CI −1.72 to 1.48; n=3976, very low-certainty evidence). Prabhakaran 2019 measured depression scores at follow-up using the Patient Health Questionnaire-9 and reported no difference between groups (MD -1.6; 95%CI -4.4 to 1.2; n=3324, very low-certainty evidence).

Quality of life: Results from one RCT[43] suggest that interventions to promote integrated care compared to usual care may make little or no difference to quality of life, but the evidence is very uncertain. The RCT reported on the change in health-related quality of life from baseline to follow-up using the EuroQol-5D visual analogue scale and the EuroQol-5D index score. There was no difference between groups, neither for the Euro-Qol-5D visual analogue scale (MD 6.06; 95%CI -3.25 to 15.36; n=3969, very low- certainty evidence) nor for the EuroQol-5D index score (MD 0.00; 95%CI -0.05 to 0.06; n=3969, very low-certainty evidence).

Table 4: Summary of findings for interventions to promote integrated delivery of care compared to usual care for diabetes and hypertension in LMICs

Patient or population: Patients with diabetes, hypertension and other chronic diseases
Setting: Low- and middle-income countries
Intervention: Strategies to promote integrated care
Comparison: Usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care	Risk with Strategies to promote integrated care				
Mortality	29 per 1,000	**32 per 1,000** (23 to 45)	**RR 1.11** (0.79 to 1.56)	4393 (1 RCT)	⨁ ◯ ◯ ◯ VERY LOW [a,b,c]	Integrated care compared to usual care may make little or no difference to the risk of death, but the evidence is very uncertain
Depression	10-item Center for Epidemiologic Studies Depression Scale: MD −0.12 (−1.72 to 1.48)			7293 (2 RCTs)	⨁ ◯ ◯ ◯ VERY LOW [a,b,c]	Integrated care compared to usual care may make little or no difference to depression scores, but the evidence is very uncertain
	Patient Health Questionnaire-9: MD -1.6 (-4.4 to 1.2)					
Change in quality of life (Euro-Qol-5D visual analogue scale)	Quality of life scores with usual care improved by a mean of 6.4 points	The mean change in quality of life with integrated care was **6.06 points higher** (3.25 points lower to 15.36 points higher)	-	3969 (1 RCT)	⨁ ◯ ◯ ◯ VERY LOW [a,b,c]	Integrated care compared to usual care may make little or no difference in quality of life, but the evidence is very uncertain
Change in HbA1c	The mean change in HbA1c with usual care ranged from -0.58 to -0.2%	The mean change in HbA1c with integrated care was **0.11 % higher** (0.2 lower to 0.42 higher)	-	1687 (2 RCTs)	⨁⨁ ◯ ◯ LOW [a,c]	Integrated care compared to usual care may have little or no effect on HbA1c
Change in systolic BP	The mean change in systolic BP with usual care ranged from -13.7 to -1.1 mmHg	The mean change in BP with integrated care was **1.11 mmHg higher** (1.14 lower to 3.35 higher)	-	4807 (2 RCTs)	⨁⨁ ◯ ◯ LOW [a,c]	Integrated care compared to usual care may have little or no effect on systolic BP

Change in total cholesterol	The mean change in total cholesterol with usual care was 2.0 mg/dl	The mean change in total cholesterol with integrated care was **2.5 mg/dl lower** (7.1 lower to 2.1 higher)	-	3324 (1 RCT)	⊕⊕ ◯ ◯ LOW [a,c]	Integrated care compared to usual care may have little or no effect on total cholesterol levels

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **BP**: Blood pressure; **HbA1c**: Glycated haemoglobin; **RCT**: Randomised controlled trial
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Footnotes: Explanation of GRADE certainty of evidence

a. Downgraded by 1 due to study limitations: high risk of performance bias and unclear risk of bias in some other domains
b. Downgraded by 1 due to imprecision: study not adequately powered for this outcome, small sample size and wide 95% CI
c. Downgraded by 1 due to indirectness: The interventions comprised strategies to promote integrated care at clinic level, and not integrated models of healthcare delivery at health system level

HbA1C: Results from two cluster RCTs[43 44] suggest that interventions to promote integrated care compared to usual care may have little or no effect on change in HbA1c from baseline to follow-up (MD 0.11%; 95%CI -0.20 to 0.42; n=1687; 2 RCTs, low-certainty evidence).

Systolic BP: Results from two cluster RCTs[43 44] suggest that interventions to promote integrated care compared to usual care may have little or no effect on change in systolic BP from baseline to follow-up (MD 1.11mmHg; 95%CI -1.41 to 3.35; n=4807; 2 RCTs, low-certainty evidence).

Total cholesterol: Results from one cluster RCT[44] suggest that interventions to promote integrated care compared to usual care may have little or no effect on change in total cholesterol from baseline to follow-up (MD -2.50mg/dl; 95%CI -7.10 to 2.10; n=3324; low-certainty evidence). The mean change in total cholesterol with usual care was 2.0 mg/dl higher.

Retention in care: Fairall 2016 reported the number of clinic visits three months before the follow-up interview and found no difference between groups (incidence rate ratio 1.02; 95%CI 0.93 to 1.13; n=3121).

Adherence: One cluster RCT reported absolute numbers for drug adherence during the past seven days.[44] Patients in the intervention group reported greater adherence for both hypertensive drugs (833/1027; 81.1% vs. 648/1119; 57.9%) and anti-hyperglycemic drugs (683/829; 82.4% vs. 570/827; 68.9%) compared to patients receiving usual care.

Quality of care: One cluster RCT[44] reported on perceived change in quality of care as a composite perception on availability of drugs, guidance from physicians, quality of care, frequency of blood pressure measurement, and care provided by NCD nurses. Perceived quality of care improved in both groups. Patients receiving integrated care (n=1637), reported that quality of care was slightly/much better (96.6%), about the same (3.3%) and somewhat/much worse (0.2%).

Patients receiving usual care (n=1687) reported that quality of care was slightly/much better (95%), about the same (4.4%) and somewhat/much worse (0.5%).

Neither of the two cluster RCTs included in this comparison reported on access to care, continuity of care or cost of care.

Discussion

Summary of main results

We included five studies and two comparisons in this review. Three studies were conducted in South Africa, one in India and one in Kenya and Uganda. Two ITS studies and one cluster RCT provided data for the first comparison, integrated models of care compared to usual care. Results suggest that integrated models of care compared to usual care may make little or no difference to mortality, the number of people achieving BP or diabetes control, and access to care; may increase the number of people who achieve both HIV and BP/diabetes control; and may have a very small effect on achieving HIV control. However, the evidence for all outcomes is very uncertain. Two cluster RCTs provided data for the second comparison, interventions to promote integrated delivery of care compared to usual care. Results suggest that interventions to promote integrated delivery of care compared to usual care may make little or no difference to mortality, depression and quality of life, but the evidence is very uncertain. Interventions to promote integrated delivery of care compared to usual care may have little or no effect on HbA1c, systolic BP, and total cholesterol levels. Process outcomes were poorly reported across included studies, with none of the studies reporting on continuity of care or cost of care.

Agreements and disagreements with other reviews

Other systematic reviews that assessed the effects of integrated models of care on health outcomes in LMICs had similar findings. Dudley and Garner[30] assessed strategies to integrate PHC services on healthcare delivery and health status in LMICs. They found no evidence that integrated services improved healthcare delivery or health status. However, none of the included studies assessed integrated care for NCDs. Haldane and colleagues[28] described existing integrated models of care for HIV and NCDs and assessed health outcomes, barriers and facilitators. However, most of the included studies were descriptive or observational and health outcomes were poorly reported. Indeed, they highlighted the need for rigorous research that includes long-term follow-up and the role of incentives.

Overall completeness and applicability of evidence

Although we considered multi-morbidity in terms of diabetes and/or hypertension plus any other disease, four out of five studies were conducted in sub-Saharan Africa and included people with diabetes and/or hypertension (and other NCDs) and HIV. All studies were conducted in rural settings. Due to successful transformation of the health systems to deliver HIV programmes, sub-Saharan Africa is presented with a unique opportunity to leverage the investments made in order to scale-up NCD services. This can be achieved in various ways, such as integrating NCD services into facilities originally providing HIV care only, integrating HIV care into PHC facilities that offer NCD care, or concurrent introduction of HIV and NCD services.[8] However, even though this is recognised, there are still questions linked to the implementation of integrated models of care. In South Africa, the ICDM model, the intervention evaluated in the ITS study by Ameh and colleagues,[42] is one example where the vertical HIV programme was integrated into general PHC facilities. As part of the pilot programme, Ameh and colleagues not only evaluated the impact on health outcomes, but also conducted a qualitative study to explore the perspectives of healthcare providers and patients on the quality of care in the ICDM model.[53] They found that PHC facilities experienced BP drug stock-outs, lack of functioning BP machines and staff shortages, among others, which impacted on the delivery of care

and indirectly therefore on the health outcomes. Integrated NCD and HIV care is implemented to a varying degree in other sub-Saharan African countries. A study examining policies and programmes for integrated HIV and NCD care in Malawi, Kenya, South Africa and Swaziland found that these countries still experience challenges in implementing integrated care. Some of these are related to inadequate data to determine the burden of NCDs among PLHIV at a local level, lack of evidence to support the implementation of integrated care models, inadequate stakeholder engagement, lack of NCD care capacity and other health system challenges.[54]

Our definition of integrated care was based on a "one-stop-shop" model whereby a patient receives all necessary care or services under one roof by one or more health-care professional (Figure 1), which is just one way of describing integrated care. Indeed, a narrative review by Njuguna, et al. [55] aimed to describe various models of integrated care for HIV and NCDs in sub-Saharan Africa. Based on the definition by WHO, the authors defined integrated care as the "coordination, co-location, or simultaneous delivery of HIV and NCD services to patients who need it, when they need it" and identified five models. These include community-based integrated HIV and NCD screening in the general population; screening for NCD risk factors among PLHIV; integrated care for HIV and NCDs in healthcare facilities through leveraging the HIV infrastructure to manage NCDs; differential care for people well-controlled HIV or NCDs, which includes longer follow-up periods for stable patients; and population health for all patients with any need.[55]

Strengths and limitations

We followed a rigorous and systematic process according to standard systematic review methods. We performed a comprehensive search of published and unpublished studies up to 12 December 2019, with no language restrictions. We purposefully included study designs that are able to provide reliable evidence on the effects of integrated care on health and process outcomes, and followed guidance provided by Cochrane EPOC. We assessed the certainty of evidence using the GRADE approach across outcomes, taking into consideration study limitations, inconsistency, imprecision, publication bias and indirectness when downgrading the certainty of evidence.

Integration of care for NCDs and HIV or other diseases is complex, partly due to the complex nature of health systems.[56] We aimed to compare fully integrated models of care to partially integrated models of care or stand-alone care. However, it was difficult to classify interventions according to our pre-specified definitions and we thus lumped interventions that integrated service delivery as 'integrated models of care'. We included two cluster RCTs that aimed to promote integrated delivery of care through clinical management tools, which is different from integrated care at facility level. We discussed this within our team and concluded that the aim of these interventions was to provide care in a holistic way and to address all the needs of an individual when s/he presents to a healthcare facility, and thus met our eligibility criteria. Furthermore, included studies did not provide adequate information on the level of integration in comparisons, but rather referred to these as standard or usual care. While these referred to a lesser degree of integration compared to the interventions, we were not able to categorise these as either partially integrated care or stand-alone care.

Our review focused on the effectiveness of integrating care for people with diabetes, hypertension and other co-morbidities in terms of health outcomes, which is just one question that needs to be answered. In other words, the question of our review focused on one building block of health systems as described by the WHO.[56] Although we aimed to examine process outcomes, these were limited to access to care, retention in care, adherence, continuity of care, quality of care and cost of care; and were poorly reported across included studies. The scope of our review did not include outcomes related to implementation or perspectives from health providers and patients, which are important aspects to consider. Although the literature predominantly highlights the need to integrate NCD and

HIV care, integrating mental health services into existing NCD and or HIV services is just as important. Four[48-51] of the five ongoing studies that we identified examine integration of mental health with NCDs.

Conclusion

The evidence on the effectiveness of integrated models of care for people with diabetes, hypertension and other co-morbidities, on health outcomes is very uncertain. We therefore do not know whether integrated models of care lead to better or worse outcomes, or may make no difference at all among people with diabetes, hypertension and other chronic conditions. There is a need to scale-up NCD services, particularly in LMICs. In the context of an increasing burden of NCDs against a backdrop of other chronic diseases, and scarce health system resources, such as human capacity and funding, policies and programmes need to promote integrated models of care and holistic, patient-centred services. However, these need to take into consideration context-specific factors related to the health system and the targeted population.

Further rigorous studies assessing the effects of integrated models of care on health outcomes are needed. These studies should include an adequate description of the integrated model of care, assess long term health effects as well as patient important outcomes, and cost of care. Furthermore, there is a need to conduct implementation research, economic evaluations as well as qualitative research on the barriers and facilitators to integrated models of care at patient and health-system level in order to guide policy makers in planning and allocation of resources in order to maximise the potential benefits of integrated care as well strengthening the health systems in achieving universal health coverage in LMICs.

Authors' contributions

All authors contributed to development of the review protocol. JUN and AR screened titles and abstracts; JUN, AR, TY and CMB participated in full text screening; TY, JJM and IT helped to resolve discrepancies. AR, JUN and IT extracted data and assessed risk of bias. AR and IT assessed certainty of evidence with input from TY and JJM. TY and JJM provided overall methodological guidance. JUN drafted the background and discussion sections, AR drafted the rest of the manuscript. JUN, IT, TY, and CMB critically read and revised the manuscript. All authors have approved the final version of the manuscript.

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Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information.

Ethics Approval

This systematic review does not involve human participants. All data included are in the public domain and ethics approval was thus not sought.

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Competing interests statement

All authors have no known conflict of interest.

Protocol

Uwimana Nicol J, Rohwer A, Young T, et al. Integrated models of care for diabetes and hypertension in low- and middle-income countries (LMICs): Protocol for a systematic review. *Syst Rev* 2018;7(1):203. doi: 10.1186/s13643-018-0865-8 [published Online First: 2018/11/22]

Figures

Figure 1: Logic model of integrated care

Figure 2: PRISMA flow diagram

Figure 3: Risk of bias in ITS studies

Figure 4: Risk of bias for cluster RCTs

Supplementary files

Supplementary file 1: Search strategies for all databases

Supplementary file 2: Table of excluded studies

Supplementary file 3: Summary of interventions according to the TIDiER checklist: Integrated models of care

Supplementary file 4: Summary of interventions according to the TIDiER checklist: Interventions to promote integrated delivery of care

Supplementary file 5: Risk of bias assessments for included studies

Supplementary file 6: Forest plots

- Please ensure to provide ethics approval statement in main document file with a heading ‘Ethics Approval’. It should be the same as stated in the ScholarOne system including the approval number (if any), if there’s none, please provide an explanation.

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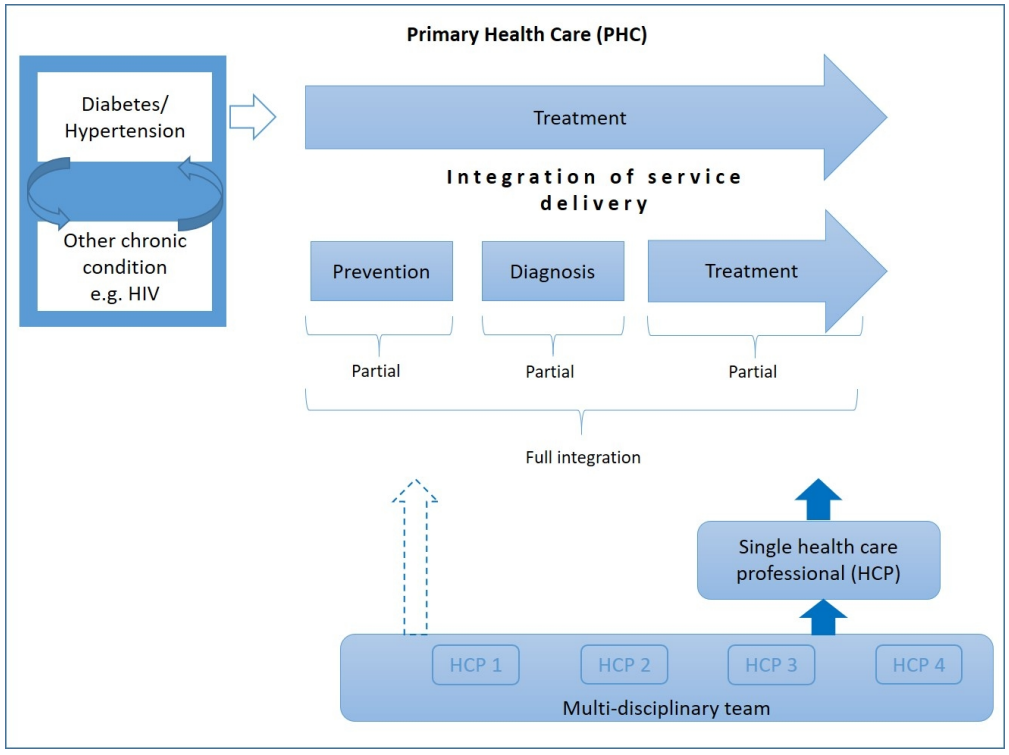

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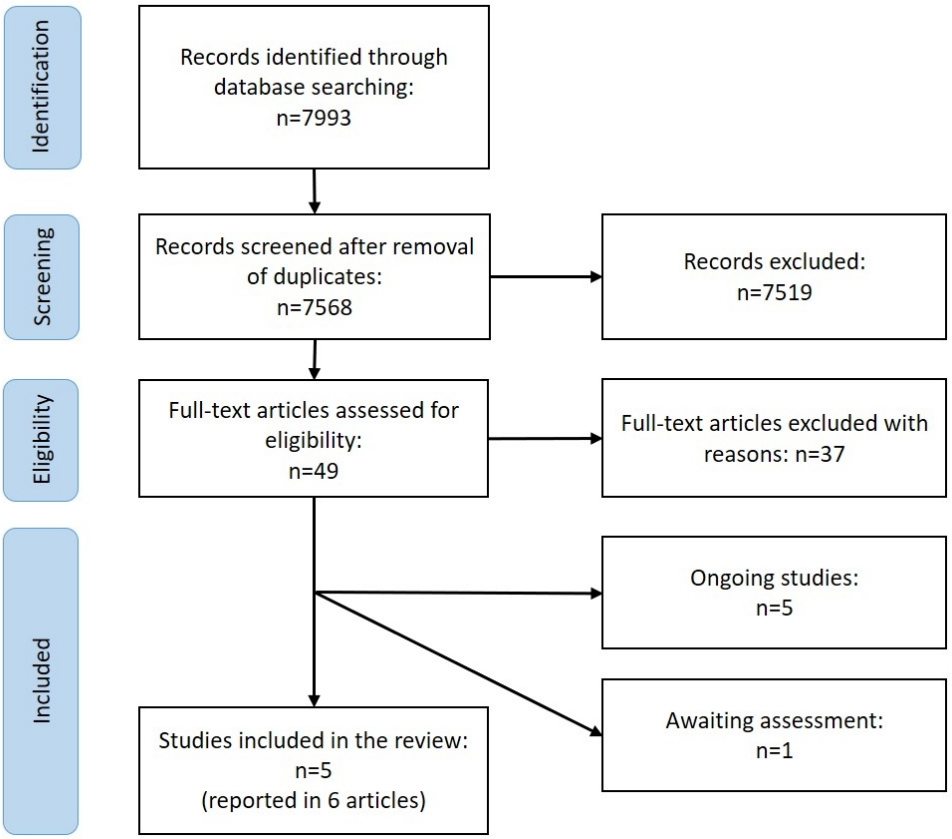
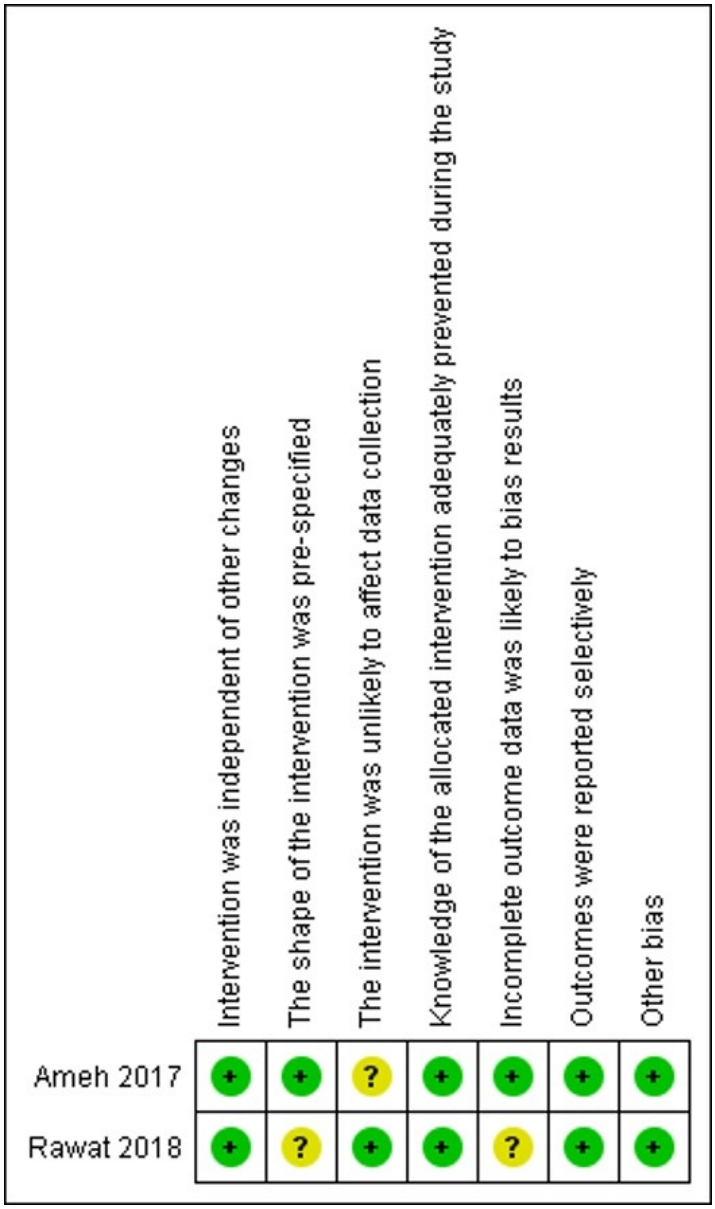


85x76mm (300 x 300 DPI)



44x75mm (300 x 300 DPI)

98x73mm (300 x 300 DPI)

Supplementary file 1: Search strategies for electronic databases

1. Medline (PubMed) search strategy

#1 "Hypertension"[Mesh] OR (hypertension OR hypertention OR "blood pressure" OR “arterial pressure” OR systolic OR diastolic)[title/abstract]

#2 diabetes OR "diabetes mellitus")[title/abstract] OR "Diabetes Mellitus"[Mesh])

#3 #1 OR #2

#4 (dyslipidaemia OR dyslipidemia OR cholesterol OR LDL OR HDL OR triglyceride OR triglycerides OR low density lipoprotein OR high density lipoprotein OR low-density lipoprotein OR high-density lipoprotein)[title/abstract] OR "Dyslipidemias"[Mesh]

#5 ((((HIV OR hiv-1 OR hiv-2* OR hiv1 OR hiv2 OR hiv infect* OR human immunodeficiency virus OR human immune deficiency virus OR human immuno-deficiency virus OR human immune-deficiency virus OR ((human immun*) AND (deficiency virus)) OR acquired immunodeficiency syndromes OR acquired immune deficiency syndrome OR acquired immuno-deficiency syndrome OR acquired immune-deficiency syndrome OR ((acquired immun*) AND (deficiency syndrome)) OR HIV/AIDS)))) OR ((HIV infections [MeSH] OR HIV [MeSH]))

#6 (tuberculosis OR tuberculoses OR tb)[Title/Abstract] OR "tuberculosis"[Mesh]

#7 "noncommunicable disease" OR "noncommunicable diseases" OR "non-communicable disease" OR "non-communicable diseases" OR NCD OR NCDs OR "Noncommunicable Diseases"[Mesh]

#8 (comorbid* OR co-morbid* OR "co morbidity" OR multimorbidity OR multi-morbid OR "multi morbidity")[title/abstract] OR "Multimorbidity"[Mesh] OR "Comorbidity"[Mesh]

#9 multi-disease* OR multidisease* OR multi disease* OR multiple condition* OR multi-condition* OR multi condition* OR multiple illness* OR multi-illness* OR multi illness* OR multiple syndrome* OR multi-syndrome* OR multi syndrome* OR concurrent condition* OR concurrent illness* OR concurrent disease* OR co-existing disease* OR coexisting disease* OR co-existing illness* OR coexisting illness* OR co-existing syndrome* OR coexisting syndrome* OR co-existing condition* OR coexisting condition* OR co-occurring disease* OR co occuring disease* OR cooccuring disease* OR co-occurring illness* OR co occurring illness* OR cooccurring illness* OR co-occurring syndrome* OR co occurring syndrome* OR cooccurring syndrome* OR co-occurring condition* OR co occurring condition* OR cooccurring condition*

#10 chronic disease* OR lifestyle disease* OR "diseases of lifestyle" OR "disease of lifestyle" OR "Multiple Chronic Conditions"[Mesh] OR "Chronic Disease"[Mesh]

#11 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

#12 "Delivery of Health Care, Integrated"[Mesh] OR “delivery of care” OR “delivery of health” OR "delivery of healthcare" OR "Comprehensive Health Care"[Mesh] OR "comprehensive healthcare" OR "comprehensive care" OR "comprehensive health" OR "Continuity of Patient Care"[Mesh] OR "continuity of patient care" OR "continuity of care" OR "continuity of health" OR "continuity of healthcare" OR "Patient-Centered Care"[Mesh] OR "patient centered care" OR "patient centred care"

#13 "Referral and Consultation"[Mesh] OR (referral AND consultation)

#14 integrat* care OR "integration of care" OR integrat* services OR "integration of services" OR integrat* programmes OR integrat* programs OR “integration of programmes” OR “integration of

programs" OR integrat* service delivery OR "integration of service delivery" OR integrat* services OR "integration of services" OR integrat* delivery OR integrat* management OR "integration of management"

#15 coordinat* care OR "coordination of care" OR coordinat* services OR "coordination of services" OR coordinat* programmes OR coordinat* programs OR "coordination of programmes" OR "coordination of programs" OR coordinat* service delivery OR "coordination of service delivery" OR coordinat* services OR "coordination of services" OR coordinat* delivery OR coordinat* management OR "coordination of management"

#16 co-ordinat* care OR "co-ordination of care" OR co-ordinat* services OR "co-ordination of services" OR co-ordinat* programmes OR co-ordinat* programs OR "co-ordination of programmes" OR "co-ordination of programs" OR co-ordinat* service delivery OR "co-ordination of service delivery" OR co-ordinat* services OR "co-ordination of services" OR co-ordinat* delivery OR co-ordinat* management OR "co-ordination of management"

#17 horizontal care OR vertical care OR horizontal services OR vertical services OR horizontal programmes OR horizontal programs OR vertical programmes OR vertical programs OR horizontal service delivery OR vertical service delivery OR horizontal services OR vertical services OR horizontal delivery OR vertical management OR vertical management

#18 "multi team" OR multiteam "multi care" OR multicare OR "multi clinic" OR multiclinic OR "multi service" OR multiservice OR "multi program" OR multiprogram OR "multi programme" OR "multi delivery" OR multidelivery OR "multi management"

#19 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18

#20 #3 AND #11 AND #19

#21 Developing Countries[Mesh:noexp] OR Africa[Mesh:noexp] OR Africa, Northern[Mesh:noexp] OR Africa South of the Sahara[Mesh:noexp] OR Africa, Central[Mesh:noexp] OR Africa, Eastern[Mesh:noexp] OR Africa, Southern[Mesh:noexp] OR Africa, Western[Mesh:noexp] OR Asia[Mesh:noexp] OR Asia, Central[Mesh:noexp] OR Asia, Southeastern[Mesh:noexp] OR Asia, Western[Mesh:noexp] OR Caribbean Region[Mesh:noexp] OR West Indies[Mesh:noexp] OR South America[Mesh:noexp] OR Latin America[Mesh:noexp] OR Central America[Mesh:noexp] OR Afghanistan[Mesh:noexp] OR Albania[Mesh:noexp] OR Algeria[Mesh:noexp] OR American Samoa[Mesh:noexp] OR Angola[Mesh:noexp] OR "Antigua and Barbuda"[Mesh:noexp] OR Argentina[Mesh:noexp] OR Armenia[Mesh:noexp] OR Azerbaijan[Mesh:noexp] OR Bahrain[Mesh:noexp] OR Bangladesh[Mesh:noexp] OR Barbados[Mesh:noexp] OR Benin[Mesh:noexp] OR Byelarus[Mesh:noexp] OR Belize[Mesh:noexp] OR Bhutan[Mesh:noexp] OR Bolivia[Mesh:noexp] OR Bosnia-Herzegovina[Mesh:noexp] OR Botswana[Mesh:noexp] OR Brazil[Mesh:noexp] OR Bulgaria[Mesh:noexp] OR Burkina Faso[Mesh:noexp] OR Burundi[Mesh:noexp] OR Cambodia[Mesh:noexp] OR Cameroon[Mesh:noexp] OR Cape Verde[Mesh:noexp] OR Central African Republic[Mesh:noexp] OR Chad[Mesh:noexp] OR Chile[Mesh:noexp] OR China[Mesh:noexp] OR Colombia[Mesh:noexp] OR Comoros[Mesh:noexp] OR Congo[Mesh:noexp] OR Costa Rica[Mesh:noexp] OR Cote d'Ivoire[Mesh:noexp] OR Croatia[Mesh:noexp] OR Cuba[Mesh:noexp] OR Cyprus[Mesh:noexp] OR Czechoslovakia[Mesh:noexp] OR Czech Republic[Mesh:noexp] OR Slovakia[Mesh:noexp] OR Djibouti[Mesh:noexp] OR "Democratic Republic of the Congo"[Mesh:noexp] OR Dominica[Mesh:noexp] OR Dominican Republic[Mesh:noexp] OR East Timor[Mesh:noexp] OR Ecuador[Mesh:noexp] OR Egypt[Mesh:noexp] OR El Salvador[Mesh:noexp] OR Eritrea[Mesh:noexp] OR Estonia[Mesh:noexp] OR Ethiopia[Mesh:noexp] OR Fiji[Mesh:noexp] OR Gabon[Mesh:noexp] OR Gambia[Mesh:noexp] OR "Georgia (Republic)"[Mesh:noexp] OR Ghana[Mesh:noexp] OR

Greece[Mesh:noexp] OR Grenada[Mesh:noexp] OR Guatemala[Mesh:noexp] OR Guinea[Mesh:noexp] OR Guinea-Bissau[Mesh:noexp] OR Guam[Mesh:noexp] OR Guyana[Mesh:noexp] OR Haiti[Mesh:noexp] OR Honduras[Mesh:noexp] OR Hungary[Mesh:noexp] OR India[Mesh:noexp] OR Indonesia[Mesh:noexp] OR Iran[Mesh:noexp] OR Iraq[Mesh:noexp] OR Jamaica[Mesh:noexp] OR Jordan[Mesh:noexp] OR Kazakhstan[Mesh:noexp] OR Kenya[Mesh:noexp] OR Korea[Mesh:noexp] OR Kosovo[Mesh:noexp] OR Kyrgyzstan[Mesh:noexp] OR Laos[Mesh:noexp] OR Latvia[Mesh:noexp] OR Lebanon[Mesh:noexp] OR Lesotho[Mesh:noexp] OR Liberia[Mesh:noexp] OR Libya[Mesh:noexp] OR Lithuania[Mesh:noexp] OR Macedonia[Mesh:noexp] OR Madagascar[Mesh:noexp] OR Malaysia[Mesh:noexp] OR Malawi[Mesh:noexp] OR Mali[Mesh:noexp] OR Malta[Mesh:noexp] OR Mauritania[Mesh:noexp] OR Mauritius[Mesh:noexp] OR Mexico[Mesh:noexp] OR Micronesia[Mesh:noexp] OR Middle East[Mesh:noexp] OR Moldova[Mesh:noexp] OR Mongolia[Mesh:noexp] OR Montenegro[Mesh:noexp] OR Morocco[Mesh:noexp] OR Mozambique[Mesh:noexp] OR Myanmar[Mesh:noexp] OR Namibia[Mesh:noexp] OR Nepal[Mesh:noexp] OR Netherlands Antilles[Mesh:noexp] OR New Caledonia[Mesh:noexp] OR Nicaragua[Mesh:noexp] OR Niger[Mesh:noexp] OR Nigeria[Mesh:noexp] OR Oman[Mesh:noexp] OR Pakistan[Mesh:noexp] OR Palau[Mesh:noexp] OR Panama[Mesh:noexp] OR Papua New Guinea[Mesh:noexp] OR Paraguay[Mesh:noexp] OR Peru[Mesh:noexp] OR Philippines[Mesh:noexp] OR Poland[Mesh:noexp] OR Portugal[Mesh:noexp] OR Puerto Rico[Mesh:noexp] OR Romania[Mesh:noexp] OR Russia[Mesh:noexp] OR "Russia (Pre-1917)"[Mesh:noexp] OR Rwanda[Mesh:noexp] OR "Saint Kitts and Nevis"[Mesh:noexp] OR Saint Lucia[Mesh:noexp] OR "Saint Vincent and the Grenadines"[Mesh:noexp] OR Samoa[Mesh:noexp] OR Saudi Arabia[Mesh:noexp] OR Senegal[Mesh:noexp] OR Serbia[Mesh:noexp] OR Montenegro[Mesh:noexp] OR Seychelles[Mesh:noexp] OR Sierra Leone[Mesh:noexp] OR Slovenia[Mesh:noexp] OR Sri Lanka[Mesh:noexp] OR Somalia[Mesh:noexp] OR South Africa[Mesh:noexp] OR Sudan[Mesh:noexp] OR Suriname[Mesh:noexp] OR Swaziland[Mesh:noexp] OR Syria[Mesh:noexp] OR Tajikistan[Mesh:noexp] OR Tanzania[Mesh:noexp] OR Thailand[Mesh:noexp] OR Togo[Mesh:noexp] OR Tonga[Mesh:noexp] OR "Trinidad and Tobago"[Mesh:noexp] OR Tunisia[Mesh:noexp] OR Turkey[Mesh:noexp] OR Turkmenistan[Mesh:noexp] OR Uganda[Mesh:noexp] OR Ukraine[Mesh:noexp] OR Uruguay[Mesh:noexp] OR USSR[Mesh:noexp] OR Uzbekistan[Mesh:noexp] OR Vanuatu[Mesh:noexp] OR Venezuela[Mesh:noexp] OR Vietnam[Mesh:noexp] OR Yemen[Mesh:noexp] OR Yugoslavia[Mesh:noexp] OR Zambia[Mesh:noexp] OR Zimbabwe[Mesh:noexp]

#22 Macedonia[tw] OR Madagascar[tw] OR Malagasy Republic[tw] OR Malaysia[tw] OR Malaya[tw] OR Malay[tw] OR Sabah[tw] OR Sarawak[tw] OR Malawi[tw] OR Nyasaland[tw] OR Mali[tw] OR Malta[tw] OR Marshall Islands[tw] OR Mauritania[tw] OR Mauritius[tw] OR Agalega Islands[tw] OR Mexico[tw] OR Micronesia[tw] OR Middle East[tw] OR Moldova[tw] OR Moldovia[tw] OR Moldovian[tw] OR Mongolia[tw] OR Montenegro[tw] OR Morocco[tw] OR Ifni[tw] OR Mozambique[tw] OR Myanmar[tw] OR Myanma[tw] OR Burma[tw] OR Namibia[tw] OR Nepal[tw] OR Netherlands Antilles[tw] OR New Caledonia[tw] OR Nicaragua[tw] OR Niger[tw] OR Nigeria[tw] OR Northern Mariana Islands[tw] OR Oman[tw] OR Muscat[tw] OR Pakistan[tw] OR Palau[tw] OR Palestine[tw] OR Panama[tw] OR Paraguay[tw] OR Peru[tw] OR Philippines[tw] OR Philipines[tw] OR Phillipines[tw] OR Phillippines[tw] OR Poland[tw] OR Portugal[tw] OR Puerto Rico[tw] OR Romania[tw] OR Rumania[tw] OR Roumania[tw] OR Russia[tw] OR Russian[tw] OR Rwanda[tw] OR Ruanda[tw] OR Saint Kitts[tw] OR St Kitts[tw] OR Nevis[tw] OR Saint Lucia[tw] OR St Lucia[tw] OR Saint Vincent[tw] OR St Vincent[tw] OR Grenadines[tw] OR Samoa[tw] OR Samoan Islands[tw] OR Navigator Island[tw] OR Navigator Islands[tw] OR Sao Tome[tw] OR Saudi Arabia[tw] OR Senegal[tw] OR Serbia[tw] OR Montenegro[tw] OR Seychelles[tw] OR Sierra Leone[tw] OR Slovenia[tw] OR Sri Lanka[tw] OR Ceylon[tw] OR Solomon Islands[tw] OR Somalia[tw] OR Sudan[tw] OR Suriname[tw] OR Surinam[tw] OR Swaziland[tw] OR Syria[tw] OR Tajikistan[tw] OR Tadzhikistan[tw] OR Tadjikistan[tw]

OR Tadzhik[tw] OR Tanzania[tw] OR Thailand[tw] OR Togo[tw] OR Togolese Republic[tw] OR Tonga[tw] OR Trinidad[tw] OR Tobago[tw] OR Tunisia[tw] OR Turkey[tw] OR Turkmenistan[tw] OR Turkmen[tw] OR Uganda[tw] OR Ukraine[tw] OR Uruguay[tw] OR USSR[tw] OR Soviet Union[tw] OR Union of Soviet Socialist Republics[tw] OR Uzbekistan[tw] OR Uzbek OR Vanuatu[tw] OR New Hebrides[tw] OR Venezuela[tw] OR Vietnam[tw] OR Viet Nam[tw] OR West Bank[tw] OR Yemen[tw] OR Yugoslavia[tw] OR Zambia[tw] OR Zimbabwe[tw] OR Rhodesia[tw]

#23 Africa[tw] OR Asia[tw] OR Caribbean[tw] OR West Indies[tw] OR South America[tw] OR Latin America[tw] OR Central America[tw] OR Afghanistan[tw] OR Albania[tw] OR Algeria[tw] OR Angola[tw] OR Antigua[tw] OR Barbuda[tw] OR Argentina[tw] OR Armenia[tw] OR Armenian[tw] OR Aruba[tw] OR Azerbaijan[tw] OR Bahrain[tw] OR Bangladesh[tw] OR Barbados[tw] OR Benin[tw] OR Byelarus[tw] OR Byelorussian[tw] OR Belarus[tw] OR Belorussian[tw] OR Belorussia[tw] OR Belize[tw] OR Bhutan[tw] OR Bolivia[tw] OR Bosnia[tw] OR Herzegovina[tw] OR Hercegovina[tw] OR Botswana[tw] OR Brasil[tw] OR Brazil[tw] OR Bulgaria[tw] OR Burkina Faso[tw] OR Burkina Fasso[tw] OR Upper Volta[tw] OR Burundi[tw] OR Urundi[tw] OR Cambodia[tw] OR Khmer Republic[tw] OR Kampuchea[tw] OR Cameroon[tw] OR Cameroons[tw] OR Cameron[tw] OR Camerons[tw] OR Cape Verde[tw] OR Central African Republic[tw] OR Chad[tw] OR Chile[tw] OR China[tw] OR Colombia[tw] OR Comoros[tw] OR Comoro Islands[tw] OR Comores[tw] OR Mayotte[tw] OR Congo[tw] OR Zaire[tw] OR Costa Rica[tw] OR Cote d'Ivoire[tw] OR Ivory Coast[tw] OR Croatia[tw] OR Cuba[tw] OR Cyprus[tw] OR Czechoslovakia[tw] OR Czech Republic[tw] OR Slovakia[tw] OR Slovak Republic[tw] OR Djibouti[tw] OR French Somaliland[tw] OR Dominica[tw] OR Dominican Republic[tw] OR East Timor[tw] OR East Timur[tw] OR Timor Leste[tw] OR Ecuador[tw] OR Egypt[tw] OR United Arab Republic[tw] OR El Salvador[tw] OR Eritrea[tw] OR Estonia[tw] OR Ethiopia[tw] OR Fiji[tw] OR Gabon[tw] OR Gabonese Republic[tw] OR Gambia[tw] OR Gaza[tw] OR Georgia Republic[tw] OR Georgian Republic[tw] OR Ghana[tw] OR Gold Coast[tw] OR Greece[tw] OR Grenada[tw] OR Guatemala[tw] OR Guinea[tw] OR Guam[tw] OR Guiana[tw] OR Guyana[tw] OR Haiti[tw] OR Honduras[tw] OR Hungary[tw] OR India[tw] OR Maldives[tw] OR Indonesia[tw] OR Iran[tw] OR Iraq[tw] OR Isle of Man[tw] OR Jamaica[tw] OR Jordan[tw] OR Kazakhstan[tw] OR Kazakh[tw] OR Kenya[tw] OR Kiribati[tw] OR Korea[tw] OR Kosovo[tw] OR Kyrgyzstan[tw] OR Kirghizia[tw] OR Kyrgyz Republic[tw] OR Kirghiz[tw] OR Kirgizstan[tw] OR "Lao PDR"[tw] OR Laos[tw] OR Latvia[tw] OR Lebanon[tw] OR Lesotho[tw] OR Basutoland[tw] OR Liberia[tw] OR Libya[tw] OR Lithuania[tw]

#24 "developing country"[tw] OR "developing countries"[tw] OR "developing nation"[tw] OR "developing nations"[tw] OR "developing population"[tw] OR "developing populations"[tw] OR "developing world"[tw] OR "less developed country"[tw] OR "less developed countries"[tw] OR "less developed nation"[tw] OR "less developed nations"[tw] OR "less developed population"[tw] OR "less developed populations"[tw] OR "less developed world"[tw] OR "lesser developed country"[tw] OR "lesser developed countries"[tw] OR "lesser developed nation"[tw] OR "lesser developed nations"[tw] OR "lesser developed population"[tw] OR "lesser developed populations"[tw] OR "lesser developed world"[tw] OR "under developed country"[tw] OR "under developed countries"[tw] OR "under developed nation"[tw] OR "under developed nations"[tw] OR "under developed population"[tw] OR "under developed populations"[tw] OR "under developed world"[tw] OR "underdeveloped country"[tw] OR "underdeveloped countries"[tw] OR "underdeveloped nation"[tw] OR "underdeveloped nations"[tw] OR "underdeveloped population"[tw] OR "underdeveloped populations"[tw] OR "underdeveloped world"[tw] OR "middle income country"[tw] OR "middle income countries"[tw] OR "middle income nation"[tw] OR "middle income nations"[tw] OR "middle income population"[tw] OR "middle income populations"[tw] OR "low income country"[tw] OR "low income countries"[tw] OR "low income nation"[tw] OR "low income nations"[tw] OR "low income population"[tw] OR "low income populations"[tw] OR "lower income country"[tw] OR "lower income countries"[tw] OR "lower income nation"[tw] OR "lower income nations"[tw] OR "lower income population"[tw] OR "lower income populations"[tw] OR "underserved country"[tw] OR "underserved

countries"[tw] OR "underserved nation"[tw] OR "underserved nations"[tw] OR "underserved population"[tw] OR "underserved populations"[tw] OR "underserved world"[tw] OR "under served country"[tw] OR "under served countries"[tw] OR "under served nation"[tw] OR "under served nations"[tw] OR "under served population"[tw] OR "under served populations"[tw] OR "under served world"[tw] OR "deprived country"[tw] OR "deprived countries"[tw] OR "deprived nation"[tw] OR "deprived nations"[tw] OR "deprived population"[tw] OR "deprived populations"[tw] OR "deprived world"[tw] OR "poor country"[tw] OR "poor countries"[tw] OR "poor nation"[tw] OR "poor nations"[tw] OR "poor population"[tw] OR "poor populations"[tw] OR "poor world"[tw] OR "poorer country"[tw] OR "poorer countries"[tw] OR "poorer nation"[tw] OR "poorer nations"[tw] OR "poorer population"[tw] OR "poorer populations"[tw] OR "poorer world"[tw] OR "developing economy"[tw] OR "developing economies"[tw] OR "less developed economy"[tw] OR "less developed economies"[tw] OR "lesser developed economy"[tw] OR "lesser developed economies"[tw] OR "under developed economy"[tw] OR "under developed economies"[tw] OR "underdeveloped economy"[tw] OR "underdeveloped economies"[tw] OR "middle income economy"[tw] OR "middle income economies"[tw] OR "low income economy"[tw] OR "low income economies"[tw] OR "lower income economy"[tw] OR "lower income economies"[tw] OR "low gdp"[tw] OR "low gnp"[tw] OR "low gross domestic"[tw] OR "low gross national"[tw] OR "lower gdp"[tw] OR "lower gnp"[tw] OR "lower gross domestic"[tw] OR "lower gross national"[tw] OR lmic[tw] OR lmics[tw] OR "third world"[tw] OR "lami country"[tw] OR "lami countries"[tw] OR "transitional country"[tw] OR "transitional countries"[tw]

#25 #21 OR #22 OR #23 OR #24

#26 #20 AND #25

2. CENTRAL

#1 MeSH descriptor: [Hypertension] explode all trees

#2 hypertension OR hypertention OR "blood pressure" OR “arterial pressure” OR systolic OR diastolic

#3 diabetes OR "diabetes mellitus"

#4 MeSH descriptor: [Diabetes Mellitus] explode all trees

#5 #1 OR #2 OR #3 OR #4

#6 dyslipidaemia OR dyslipidemia OR cholesterol OR LDL OR HDL OR triglyceride OR triglycerides OR "low density lipoprotein" OR "high density lipoprotein" OR "low-density lipoprotein" OR "high-density lipoprotein"

#7 MeSH descriptor: [Dyslipidemias] explode all trees

#8 HIV OR hiv-1 OR hiv-2* OR hiv1 OR hiv2 OR "hiv infection" OR "hiv infections" OR "human immunodeficiency virus" OR "human immune deficiency virus" OR "human immuno-deficiency virus" OR "human immune-deficiency virus"

#9 (human immun*) AND (deficiency virus)

#10 "acquired immunodeficiency syndromes" OR "acquired immune deficiency syndrome" OR "acquired immuno-deficiency syndrome" OR "acquired immune-deficiency syndrome"

#11 (acquired immun*) AND (deficiency syndrome)

#12 HIVAIDS

#13 MeSH descriptor: [HIV Infections] explode all trees

#14 MeSH descriptor: [HIV] explode all trees

#15 tuberculosis OR tuberculoses OR tb

#16 MeSH descriptor: [Tuberculosis] explode all trees

#17 "noncommunicable disease" OR "noncommunicable diseases" OR "non-communicable disease" OR "non-communicable diseases" OR NCD OR NCDs

#18 MeSH descriptor: [Noncommunicable Diseases] explode all trees

#19 comorbidity OR comorbidities OR comorbid OR co-morbid OR co-morbidity OR co-morbidities OR "co morbidity" OR multimorbidity OR multi-morbid OR "multi morbidity"

#20 MeSH descriptor: [Multimorbidity] explode all trees

#21 MeSH descriptor: [Comorbidity] explode all trees

#22 multi-disease* OR multidisease* OR multi disease* OR multiple condition* OR multi-condition* OR multi condition* OR multiple illness* OR multi-illness* OR multi illness* OR multiple syndrome* OR multi-syndrome* OR multi syndrome* OR concurrent condition* OR concurrent illness* OR concurrent disease* OR co-existing disease* OR coexisting disease* OR co-existing illness* OR coexisting illness* OR co-existing syndrome* OR coexisting syndrome* OR co-existing condition* OR coexisting condition* OR co-occurring disease* OR co occuring disease* OR cooccuring disease* OR co-occurring illness* OR co occurring illness* OR cooccurring illness* OR co-occurring syndrome* OR co occurring syndrome* OR cooccurring syndrome* OR co-occurring condition* OR co occurring condition* OR cooccurring condition*

#23 chronic disease* OR lifestyle disease* OR "diseases of lifestyle" OR "disease of lifestyle"

#24 MeSH descriptor: [Multiple Chronic Conditions] explode all trees

#25 MeSH descriptor: [Chronic Disease] explode all trees

#26 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25

#27 MeSH descriptor: [Delivery of Health Care, Integrated] explode all trees

#28 “delivery of care” OR “delivery of health” OR "delivery of healthcare"

#29 MeSH descriptor: [Comprehensive Health Care] explode all trees

#30 "comprehensive healthcare" OR "comprehensive care" OR "comprehensive health"

#31 MeSH descriptor: [Continuity of Patient Care] explode all trees 23230

#32 "continuity of patient care" OR "continuity of care" OR "continuity of health" OR "continuity of healthcare"

#33 MeSH descriptor: [Patient-Centered Care] explode all trees

#34 "patient centered care" OR "patient centred care"

#35 MeSH descriptor: [Referral and Consultation] explode all trees

#36 referral AND consultation

#37 integrat* care OR "integration of care" OR integrat* services OR "integration of services" OR integrat* programmes OR integrat* programs OR “integration of programmes” OR “integration of programs” OR integrat* service delivery OR “integration of service delivery” OR integrat* services OR “integration of services” OR integrat* delivery OR integrat* management OR “integration of management”

#38 coordinat* care OR "coordination of care" OR coordinat* services OR "coordination of services" OR coordinat* programmes OR coordinat* programs OR “coordination of programmes” OR “coordination of programs” OR coordinat* service delivery OR “coordination of service delivery” OR coordinat* services OR “coordination of services” OR coordinat* delivery OR coordinat* management OR “coordination of management”

#39 co-ordinat* care OR "co-ordination of care" OR co-ordinat* services OR "co-ordination of services" OR co-ordinat* programmes OR co-ordinat* programs OR “co-ordination of programmes” OR “co-ordination of programs” OR co-ordinat* service delivery OR “co-ordination of service delivery” OR co-ordinat* services OR “co-ordination of services” OR co-ordinat* delivery OR co-ordinat* management OR “co-ordination of management”

#40 "horizontal care" OR "vertical care" OR "horizontal services" OR "vertical services" OR "horizontal programmes" OR "horizontal programs" OR "vertical programmes" OR "vertical programs" OR "horizontal service delivery" OR "vertical service delivery" OR "horizontal services" OR "vertical services" OR "horizontal delivery" OR "vertical management" OR "vertical management"

#41 “multi team” OR multiteam “multi care” OR multicare OR “multi clinic” OR multiclinic OR “multi service” OR multiservice OR “multi program” OR multiprogram OR “multi programme” OR “multi delivery” OR multidelivery OR “multi management”

#42 #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41

#43 #5 AND #26 AND #42

#44 (Africa or Asia or Caribbean or "West Indies" or "South America" or "Latin America" or "Central America")

#45 (Afghanistan or Albania or Algeria or Angola or Antigua or Barbuda or Argentina or Armenia or Armenian or Aruba or Azerbaijan or Bahrain or Bangladesh or Barbados or Benin or Byelarus or Byelorussian or Belarus or Belorussian or Belorussia or Belize or Bhutan or Bolivia or Bosnia or Herzegovina or Hercegovina or Botswana or Brasil or Brazil or Bulgaria or "Burkina Faso" or "Burkina Fasso" or "Upper Volta" or Burundi or Urundi or Cambodia or "Khmer Republic" or Kampuchea or Cameroon or Cameroons or Cameron or Camerons or "Cape Verde" or "Central African Republic" or Chad or Chile or China or Colombia or Comoros or "Comoro Islands" or Comores or Mayotte or Congo or "Republic of Congo" or Zaire or "Costa Rica" or "Cote d'Ivoire" or "Ivory Coast" or Croatia or Cuba or Cyprus or Czechoslovakia or "Czech Republic" or Slovakia or "Slovak Republic")

#46 (Djibouti or "French Somaliland" or Dominica or "Dominican Republic" or "East Timor" or "East Timur" or "Timor Leste" or Ecuador or Egypt or "United Arab Republic" or "El Salvador" or Eritrea or Estonia or Ethiopia or Fiji or Gabon or "Gabonese Republic" or Gambia or Gaza or Georgia or Georgian or Ghana or "Gold Coast" or Greece or Grenada or Guatemala or Guinea or Guam or Guiana or Guyana or Haiti or Honduras or Hungary or India or Maldives or Indonesia or Iran or Iraq or "Isle of Man" or Jamaica or Jordan or Kazakhstan or Kazakh or Kenya or Kiribati or Korea or Kosovo or Kyrgyzstan or Kirghizia or "Kyrgyz Republic" or Kirghiz or Kirgizstan or "Lao PDR" or Laos or Latvia or Lebanon or Lesotho or Basutoland or Liberia or Libya or Lithuania)

#47 (Macedonia or Madagascar or "Malagasy Republic" or Malaysia or Malaya or Malay or Sabah or Sarawak or Malawi or Nyasaland or Mali or Malta or "Marshall Islands" or Mauritania or Mauritius or "Agalega Islands" or Mexico or Micronesia or "Middle East" or Moldova or Moldovia or Moldovian or Mongolia or Montenegro or Morocco or Ifni or Mozambique or Myanmar or Myanma or Burma or Namibia or Nepal or "Netherlands Antilles" or "New Caledonia" or Nicaragua or Niger or Nigeria or "Northern Mariana Islands" or Oman or Muscat or Pakistan or Palau or Palestine or Panama or Paraguay or Peru or Philippines or Philipines or Phillipines or Phillippines or Poland or Portugal or "Puerto Rico")

#48 (Romania or Rumania or Roumania or Russia or Russian or Rwanda or Ruanda or "Saint Kitts" or "St Kitts" or Nevis or "Saint Lucia" or "St Lucia" or "Saint Vincent" or "St Vincent" or Grenadines or Samoa or "Samoan Islands" or "Navigator Island" or "Navigator Islands" or "Sao Tome" or "Saudi Arabia" or Senegal or Serbia or Montenegro or Seychelles or "Sierra Leone" or Slovenia or "Sri Lanka" or Ceylon or "Solomon Islands" or Somalia or Sudan or South-sudan or Suriname or Surinam or Swaziland or Syria or Tajikistan or Tadzhikistan or Tadjikistan or Tadzhik or Tanzania or Thailand or Togo or "Togolese Republic" or Tonga or Trinidad or Tobago or Tunisia or Turkey or Turkmenistan or Turkmen or Uganda or Ukraine or Uruguay or USSR or "Soviet Union" or "Union of Soviet Socialist Republics" or Uzbekistan or Uzbek or Vanuatu or "New Hebrides" or Venezuela or Vietnam or "Viet Nam" or "West Bank" or Yemen or Yugoslavia or Zambia or Zimbabwe or Rhodesia)

#49 (developing or less* NEXT developed or "under developed" or underdeveloped or "middle income" or low* NEXT income or underserved or "under served" or deprived or poor*) NEXT (countr* or nation* or population* or world)

#50 (developing or less* NEXT developed or "under developed" or underdeveloped or "middle income" or low* NEXT income) NEXT (economy or economies)

#51 low* NEXT (gdp or gnp or "gross domestic" or "gross national")

#52 (low NEAR/3 middle NEAR/3 countr*)

#53 (lmic or lmics or "third world" or "lami country" or "lami countries")

#54 ("transitional country" or "transitional countries")

#55 #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54

#56 #43 AND #55

3. Embase

1 integrated health care system/ or integrated health care.mp.

2 *patient care/

3 ("comprehensive healthcare" or "comprehensive care" or "Continuity of Patient Care" or "continuity of care" or "continuity of healthcare" or "Patient-Centered Care").ti.

4 ("comprehensive healthcare" or "comprehensive care" or "Continuity of Patient Care" or "continuity of care" or "continuity of healthcare" or "Patient-Centered Care").ab.

5 (referral and consultation).mp.

6 ((integrated or integration) adj2 (care or services or program* or delivery or management)).ab.

7 ((integrated or integration) adj2 (care or services or program* or delivery or management)).ti.

8 ((coordination or coordinated) adj2 (care or services or program* or delivery or management)).ti.

9 ((coordination or coordinated) adj2 (care or services or program* or delivery or management)).ab.

10 ((horizontal or vertical) adj2 (care or services or program* or delivery or management)).ab.

11 ((horizontal or vertical) adj2 (care or services or program* or delivery or management)).ti.

12 (Multiteam or multi-team or multi-care or multicare or multiclinic or multiservice or multi-program* or multidelivery or multi-management).ti. or (Multiteam or multi-team or multi-care or multicare or multiclinic or multiservice or multi-program* or multidelivery or multi-management).ab.

13 *health care delivery/

14 (delivery adj2 healthcare).mp.

15 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14

16 hypertension.mp. or *hypertension/

17 (hypertension or hypertention or "blood pressure" or "arterial pressure" or systolic or diastolic).ti. or (hypertension or hypertention or "blood pressure" or "arterial pressure" or systolic or diastolic).ab.

18 diabetes.mp. or diabetes mellitus/

19 exp Neoplasms/

20 cardiovascular disease/

21 "heart disease".ti. or "heart disease*".ab.

22 *kidney disease/

23 ("kidney failure" or "renal failure" or "chronic kidney disease" or "renal disease").ti. or ("kidney failure" or "renal failure" or "chronic kidney disease" or "renal disease").ab.

24 (dyslipidaemia or dyslipidemia or cholesterol or LDL or HDL or triglyceride or triglycerides or low density lipoprotein or high density lipoprotein or low-density lipoprotein or high-density lipoprotein).ti. or (dyslipidaemia or dyslipidemia or cholesterol or LDL or HDL or triglyceride or triglycerides or low density lipoprotein or high density lipoprotein or low-density lipoprotein or high-density lipoprotein).ab.

25 HIV infection.mp. or Human immunodeficiency virus infection/

26 tuberculosis/

27 non-communicable diseases.mp. or non communicable disease/

28 comorbidity.mp. or comorbidity/

29 multimorbidity.mp. or multiple chronic conditions/

30 (multi-disease* or multidisease* or multi disease* or multiple condition* or multi-condition* or multi condition* or multiple illness* or multi-illness* or multi illness* or multiple syndrome* or multi-syndrome* or multi syndrome* or concurrent condition* or concurrent illness* or concurrent disease* or co-existing disease* or coexisting disease* or co-existing illness* or coexisting illness* or co-existing syndrome* or coexisting syndrome* or co-existing condition* or coexisting condition* or co-occurring disease* or co occuring disease* or cooccuring disease* or co-occurring illness* or co

occurring illness* or cooccurring illness* or co-occurring syndrome* or co occurring syndrome* or cooccurring syndrome* or co-occurring condition* or co occurring condition* or cooccurring condition*).ti.

31 (multi-disease* or multidisease* or multi disease* or multiple condition* or multi-condition* or multi condition* or multiple illness* or multi-illness* or multi illness* or multiple syndrome* or multi-syndrome* or multi syndrome* or concurrent condition* or concurrent illness* or concurrent disease* or co-existing disease* or coexisting disease* or co-existing illness* or coexisting illness* or co-existing syndrome* or coexisting syndrome* or co-existing condition* or coexisting condition* or co-occurring disease* or co occuring disease* or cooccuring disease* or co-occurring illness* or co occurring illness* or cooccurring illness* or co-occurring syndrome* or co occurring syndrome* or cooccurring syndrome* or co-occurring condition* or co occurring condition* or cooccurring condition*).ab.

32 (chronic disease* or lifestyle disease*).mp.

33 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32

34 15 and 33

35 developing countries.mp. or developing country/

36 (Africa or Asia or Caribbean or West Indies or South America or Latin America or Central America).mp.

37 (Afghanistan or Albania or Algeria or Angola or Antigua or Barbuda or Argentina or Armenia or Armenian or Aruba or Azerbaijan or Bahrain or Bangladesh or Barbados or Benin or Byelarus or Byelorussian or Belarus or Belorussian or Belorussia or Belize or Bhutan or Bolivia or Bosnia or Herzegovina or Hercegovina or Botswana or Brazil or Bulgaria or Burkina Faso or Burkina Fasso or Upper Volta or Burundi or Urundi or Cambodia or Khmer Republic or Kampuchea or Cameroon or Cameroons or Cameron or Camerons or Cape Verde or Central African Republic or Chad or Chile or China or Colombia or Comoros or Comoro Islands or Comores or Mayotte or Congo or Zaire or Costa Rica or Cote d'Ivoire or Ivory Coast or Croatia or Cuba or Cyprus or Czechoslovakia or Czech Republic or Slovakia or Slovak Republic or Djibouti or French Somaliland or Dominica or Dominican Republic or East Timor or East Timur or Timor Leste or Ecuador or Egypt or United Arab Republic or El Salvador or Eritrea or Estonia or Ethiopia or Fiji or Gabon or Gabonese Republic or Gambia or Gaza or Georgia Republic or Georgian Republic or Ghana or Gold Coast or Greece or Grenada or Guatemala or Guinea or Guam or Guiana or Guyana or Haiti or Honduras or Hungary or India or Maldives or Indonesia or Iran or Iraq or Isle of Man or Jamaica or Jordan or Kazakhstan or Kazakh or Kenya or Kiribati or Korea or Kosovo or Kyrgyzstan or Kirghizia or Kyrgyz Republic or Kirghiz or Kirgizstan or Lao PDR or Laos or Latvia or Lebanon or Lesotho or Basutoland or Liberia or Libya or Lithuania or Macedonia or Madagascar or Malagasy Republic or Malaysia or Malaya or Malay or Sabah or Sarawak or Malawi or Nyasaland or Mali or Malta or Marshall Islands or Mauritania or Mauritius or Agalega Islands or Mexico or Micronesia or Middle East or Moldova or Moldovia or Moldovian or Mongolia or Montenegro or Morocco or Ifni or Mozambique or Myanmar or Myanma or Burma or Namibia or Nepal or Netherlands Antilles or New Caledonia or Nicaragua or Niger or Nigeria or Northern Mariana Islands or Oman or Muscat or Pakistan or Palau or Palestine or Panama or Paraguay or Peru or Philippines or Philipines or Phillipines or Phillippines or Poland or Portugal or Puerto Rico or Romania or Rumania or Roumania or Russia or Russian or Rwanda or Ruanda or Saint Kitts or St Kitts or Nevis or Saint Lucia or St Lucia or Saint Vincent or St Vincent or Grenadines or Samoa or Samoan Islands or Navigator Island or Navigator Islands or Sao Tome or Saudi Arabia or Senegal or Serbia or Montenegro or Seychelles or Sierra Leone or Slovenia or Sri Lanka or Ceylon or Solomon Islands or Somalia or Sudan or Suriname or Surinam or Swaziland or Syria or Tajikistan or Tadzhikistan or

Tadjikistan or Tadzhik or Tanzania or Thailand or Togo or Togolese Republic or Tonga or Trinidad or Tobago or Tunisia or Turkey or Turkmenistan or Turkmen or Uganda or Ukraine or Uruguay or USSR or Soviet Union or Union of Soviet Socialist Republics or Uzbekistan or Uzbek or Vanuatu or New Hebrides or Venezuela or Vietnam or Viet Nam or West Bank or Yemen or Yugoslavia or Zambia or Zimbabwe or Rhodesia).mp.

38 ((developing or less* developed or under developed or underdeveloped or middle income or low* income or underserved or under served or deprived or poor*) adj (countr* or nation? or population? or world)).ab.

39 ((developing or less* developed or under developed or underdeveloped or middle income or low* income) adj (economy or economies)).ab. or ((developing or less* developed or under developed or underdeveloped or middle income or low* income) adj (economy or economies)).ti.

40 ((developing or less* developed or under developed or underdeveloped or middle income or low* income or underserved or under served or deprived or poor*) adj (countr* or nation? or population? or world)).ti.

41 (low* adj (gdp or gnp or gross domestic or gross national)).ti. or (low* adj (gdp or gnp or gross domestic or gross national)).ab.

42 (low adj3 middle adj3 countr*).ti. or (low adj3 middle adj3 countr*).ab.

43 (lmic or lmics or third world or lami countr*).ti. or (lmic or lmics or third world or lami countr*).ab.

44 transitional countr*.ti. or transitional countr*.ab.

45 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44

46 34 and 45

4. Web of Science (Core collection)

TOPIC: (hypertension OR hypertention OR "blood pressure" OR “arterial pressure” OR systolic OR diastolic OR diabetes OR "diabetes mellitus") AND TOPIC: (dyslipidaemia OR dyslipidemia OR cholesterol OR LDL OR HDL OR triglyceride OR triglycerides OR low density lipoprotein OR high density lipoprotein OR low-density lipoprotein OR high-density lipoprotein OR HIV OR hiv-1 OR hiv-2* OR hiv1 OR hiv2 OR hiv infect* OR "human immunodeficiency virus" OR "human immune deficiency virus" OR "human immuno-deficiency virus" OR "human immune-deficiency virus" OR "acquired immunodeficiency syndromes" OR "acquired immune deficiency syndrome" OR "acquired immuno-deficiency syndrome" OR "acquired immune-deficiency syndrome" OR HIV/AIDS OR tuberculosis OR tuberculoses OR tb OR "noncommunicable disease" OR "noncommunicable diseases" OR "non-communicable disease" OR "non-communicable diseases" OR NCD OR NCDs OR comorbid* OR co-morbid* OR "co morbidity" OR multimorbidity OR multi-morbid OR "multi morbidity" OR multi-disease* OR multidisease* OR multi disease* OR multiple condition* OR multi-condition* OR multi condition* OR multiple illness* OR multi-illness* OR multi illness* OR multiple syndrome* OR multi-syndrome* OR multi syndrome* OR concurrent condition* OR concurrent illness* OR concurrent disease* OR co-existing disease* OR coexisting disease* OR co-existing illness* OR coexisting illness* OR co-existing syndrome* OR coexisting syndrome* OR co-existing condition* OR coexisting condition* OR co-occurring disease* OR co occuring disease* OR cooccuring disease* OR co-occurring illness* OR co occurring illness* OR cooccurring illness* OR co-occurring syndrome* OR co occurring syndrome* OR cooccurring syndrome* OR co-occurring condition* OR co occurring condition* OR cooccurring condition* OR chronic disease* OR lifestyle disease* OR "diseases of

lifestyle" OR "disease of lifestyle" OR "Multiple Chronic Conditions") AND TOPIC: (“delivery of care” OR “delivery of health” OR "delivery of healthcare" OR "Comprehensive Health Care" OR "comprehensive healthcare" OR "comprehensive care" OR "comprehensive health" OR "Continuity of Patient Care" OR "continuity of patient care" OR "continuity of care" OR "continuity of health" OR "continuity of healthcare" OR "Patient-Centered Care" OR "patient centered care" OR "patient centred care" OR "Referral and Consultation" OR integrat* care OR "integration of care" OR integrat* services OR "integration of services" OR integrat* programmes OR integrat* programs OR “integration of programmes” OR “integration of programs” OR integrat* service delivery OR “integration of service delivery” OR integrat* services OR “integration of services” OR integrat* delivery OR integrat* management OR “integration of management” OR coordinat* care OR "coordination of care" OR coordinat* services OR "coordination of services" OR coordinat* programmes OR coordinat* programs OR “coordination of programmes” OR “coordination of programs” OR coordinat* service delivery OR “coordination of service delivery” OR coordinat* services OR “coordination of services” OR coordinat* delivery OR coordinat* management OR “coordination of management” OR co-ordinat* care OR "co-ordination of care" OR co-ordinat* services OR "co-ordination of services" OR co-ordinat* programmes OR co-ordinat* programs OR “co-ordination of programmes” OR “co-ordination of programs” OR co-ordinat* service delivery OR “co-ordination of service delivery” OR co-ordinat* services OR “co-ordination of services” OR co-ordinat* delivery OR co-ordinat* management OR “co-ordination of management” OR horizontal care OR vertical care OR horizontal services OR vertical services OR horizontal programmes OR horizontal programs OR vertical programmes OR vertical programs OR horizontal service delivery OR vertical service delivery OR horizontal services OR vertical services OR horizontal delivery OR vertical management OR vertical management OR “multi team” OR multiteam “multi care” OR multicare OR “multi clinic” OR multiclinic OR “multi service” OR multiservice OR “multi program” OR multiprogram OR “multi programme” OR “multi delivery” OR multidelivery OR “multi management”) AND TOPIC: (Afghanistan or Albania or Algeria or Angola or Antigua or Barbuda or Argentina or Armenia or Armenian or Aruba or Azerbaijan or Bahrain or Bangladesh or Barbados or Benin or Byelarus or Byelorussian or Belarus or Belorussian or Belorussia or Belize or Bhutan or Bolivia or Bosnia or Herzegovina or Hercegovina or Botswana or Brasil or Brazil or Bulgaria or "Burkina Faso" or "Burkina Fasso" or "Upper Volta" or Burundi or Urundi or Cambodia or "Khmer Republic" or Kampuchea or Cameroon or Cameroons or Cameron or Camerons or "Cape Verde" or "Central African Republic" or Chad or Chile or China or Colombia or Comoros or "Comoro Islands" or Comores or Mayotte or Congo or "Republic of Congo" or Zaire or "Costa Rica" or "Cote d'Ivoire" or "Ivory Coast" or Croatia or Cuba or Cyprus or Czechoslovakia or "Czech Republic" or Slovakia or "Slovak Republic" OR Djibouti or "French Somaliland" or Dominica or "Dominican Republic" or "East Timor" or "East Timur" or "Timor Leste" or Ecuador or Egypt or "United Arab Republic" or "El Salvador" or Eritrea or Estonia or Ethiopia or Fiji or Gabon or "Gabonese Republic" or Gambia or Gaza or Georgia or Georgian or Ghana or "Gold Coast" or Greece or Grenada or Guatemala or Guinea or Guam or Guiana or Guyana or Haiti or Honduras or Hungary or India or Maldives or Indonesia or Iran or Iraq or "Isle of Man" or Jamaica or Jordan or Kazakhstan or Kazakh or Kenya or Kiribati or Korea or Kosovo or Kyrgyzstan or Kirghizia or "Kyrgyz Republic" or Kirghiz or Kirgizstan or "Lao PDR" or Laos or Latvia or Lebanon or Lesotho or Basutoland or Liberia or Libya or Lithuania OR Macedonia or Madagascar or "Malagasy Republic" or Malaysia or Malaya or Malay or Sabah or Sarawak or Malawi or Nyasaland or Mali or Malta or "Marshall Islands" or Mauritania or Mauritius or "Agalega Islands" or Mexico or Micronesia or "Middle East" or Moldova or Moldovia or Moldovian or Mongolia or Montenegro or Morocco or Ifni or Mozambique or Myanmar or Myanma or Burma or Namibia or Nepal or "Netherlands Antilles" or "New Caledonia" or Nicaragua or Niger or Nigeria or "Northern Mariana Islands" or Oman or Muscat or Pakistan or Palau or Palestine or Panama or Paraguay or Peru or Philippines or Philipines or Phillipines or Phillippines or Poland or Portugal or "Puerto Rico" OR Romania or Rumania or Roumania or Russia or Russian or Rwanda or Ruanda or "Saint Kitts" or "St Kitts" or Nevis or "Saint

Lucia" or "St Lucia" or "Saint Vincent" or "St Vincent" or Grenadines or Samoa or "Samoan Islands" or "Navigator Island" or "Navigator Islands" or "Sao Tome" or "Saudi Arabia" or Senegal or Serbia or Montenegro or Seychelles or "Sierra Leone" or Slovenia or "Sri Lanka" or Ceylon or "Solomon Islands" or Somalia or Sudan or South-Sudan or Suriname or Surinam or Swaziland or Syria or Tajikistan or Tadzhikistan or Tadjikistan or Tadzhik or Tanzania or Thailand or Togo or "Togolese Republic" or Tonga or Trinidad or Tobago or Tunisia or Turkey or Turkmenistan or Turkmen or Uganda or Ukraine or Uruguay or USSR or "Soviet Union" or "Union of Soviet Socialist Republics" or Uzbekistan or Uzbek or Vanuatu or "New Hebrides" or Venezuela or Vietnam or "Viet Nam" or "West Bank" or Yemen or Yugoslavia or Zambia or Zimbabwe or Rhodesia OR "developing country" OR "gross domestic" OR "gross national" OR "low income" OR "low-income" OR "middle income" OR "middle-income" OR LMIC OR LMICs OR "transitional country" OR "transitional countries" OR "third world" OR "lami country" OR "lami countries" OR "under developed" OR underdeveloped OR under-developed)

5. CINAHL

S1 MW hypertension OR ((hypertension OR hypertention OR "blood pressure" OR “arterial pressure” OR systolic OR diastolic)) OR ((diabetes OR "diabetes mellitus")) OR MW "Diabetes Mellitus" [320,859]

S2 ((dyslipidaemia OR dyslipidemia OR cholesterol OR LDL OR HDL OR triglyceride OR triglycerides OR low density lipoprotein OR high density lipoprotein OR low-density lipoprotein OR high-density lipoprotein)) OR MW Dyslipidemias OR MW HIV OR MW HIV infections OR ((HIV OR hiv-1 OR hiv-2* OR hiv1 OR hiv2 OR hiv infect* OR "human immunodeficiency virus" OR "human immune deficiency virus" OR "human immuno-deficiency virus" OR "human immune-deficiency virus" OR "acquired immunodeficiency syndromes" OR "acquired immune deficiency syndrome" OR "acquired immuno-deficiency syndrome" OR "acquired immune-deficiency syndrome" OR HIV/AIDS)) OR ((tuberculosis OR tuberculoses OR tb)) OR MW tuberculosis OR (("noncommunicable disease" OR "noncommunicable diseases" OR "non-communicable disease" OR "non-communicable diseases" OR NCD OR NCDs)) OR MW "noncommunicable diseases" OR ((comorbid* OR co-morbid* OR "co morbidity" OR multimorbidity OR multi-morbid OR "multi morbidity")) OR MW multimorbidity OR MW comorbidity [282,133]

S3 ((multi-disease* OR multidisease* OR multi disease* OR multiple condition* OR multi-condition* OR multi condition* OR multiple illness* OR multi-illness* OR multi illness* OR multiple syndrome* OR multi-syndrome* OR multi syndrome* OR concurrent condition* OR concurrent illness* OR concurrent disease* OR co-existing disease* OR coexisting disease* OR co-existing illness* OR coexisting illness* OR co-existing syndrome* OR coexisting syndrome* OR co-existing condition* OR coexisting condition* OR co-occurring disease* OR co occuring disease* OR cooccuring disease* OR co-occurring illness* OR co occurring illness* OR cooccurring illness* OR co-occurring syndrome* OR co occurring syndrome* OR cooccurring syndrome* OR co-occurring condition* OR co occurring condition* OR cooccurring condition*)) OR ((chronic disease* OR lifestyle disease* OR "diseases of lifestyle" OR "disease of lifestyle")) OR MW "Multiple Chronic Conditions” OR MW "Chronic Disease" [141,677]

S4 S2 OR S3 [399,117]

S5 MW "Delivery of Health Care, Integrated" OR MW "Comprehensive Health Care" OR MW "Continuity of Patient Care" OR MW "Patient-Centered Care" [38488]

S6 ((“delivery of care” OR “delivery of health” OR "delivery of healthcare" OR "comprehensive healthcare" OR "comprehensive care" OR "comprehensive health" OR "continuity of patient care" OR "continuity of care" OR "continuity of health" OR "continuity of healthcare" OR "patient centered

care" OR "patient centred care") OR ((referral AND consultation)) OR MW ("Referral and Consultation") OR ((integrat* care OR "integration of care" OR integrat* services OR "integration of services" OR integrat* programmes OR integrat* programs OR “integration of programmes” OR “integration of programs” OR integrat* service delivery OR “integration of service delivery” OR integrat* services OR “integration of services” OR integrat* delivery OR integrat* management OR “integration of management”)) OR ((coordinat* care OR "coordination of care" OR coordinat* services OR "coordination of services" OR coordinat* programmes OR coordinat* programs OR “coordination of programmes” OR “coordination of programs” OR coordinat* service delivery OR “coordination of service delivery” OR coordinat* services OR “coordination of services” OR coordinat* delivery OR coordinat* management OR “coordination of management”)) OR ((co-ordinat* care OR "co-ordination of care" OR co-ordinat* services OR "co-ordination of services" OR co-ordinat* programmes OR co-ordinat* programs OR “co-ordination of programmes” OR “co-ordination of programs” OR co-ordinat* service delivery OR “co-ordination of service delivery” OR co-ordinat* services OR “co-ordination of services” OR co-ordinat* delivery OR co-ordinat* management OR “co-ordination of management”)) OR ((horizontal care OR vertical care OR horizontal services OR vertical services OR horizontal programmes OR horizontal programs OR vertical programmes OR vertical programs OR horizontal service delivery OR vertical service delivery OR horizontal services OR vertical services OR horizontal delivery OR vertical management OR vertical management)) OR ((“multi team” OR multiteam “multi care” OR multicare OR “multi clinic” OR multiclinic OR “multi service” OR multiservice OR “multi program” OR multiprogram OR “multi programme” OR “multi delivery” OR multidelivery OR “multi management”)) [145,695]

S7 S5 OR S6 [145,695]

S8 “((developing country" OR "gross domestic" OR "gross national" OR "low income" OR "low-income" OR "middle income" OR "middle-income" OR LMIC OR LMICs OR "transitional country" OR "transitional countries" OR "third world" OR "lami country" OR "lami countries" OR "under developed" OR underdeveloped OR under-developed)) OR ("low- and middle-income") OR ("low and middle income")” [32,715]

S9 S1 AND S4 AND S7 AND S8 [71]

S10 PY 2019 [381,913]

S11 PY 2018 [419,274]

S12 S10 OR S11 [801,187]

S13 S9 AND S12 [17]

6. Africa-Wide Information (via EBSCO host)

S1 SM hypertension OR (hypertension OR hypertention OR "blood pressure" OR “arterial pressure” OR systolic OR diastolic)) OR ((diabetes OR "diabetes mellitus") OR SM "Diabetes Mellitus"

S2 (dyslipidaemia OR dyslipidemia OR cholesterol OR LDL OR HDL OR triglyceride OR triglycerides OR low density lipoprotein OR high density lipoprotein OR low-density lipoprotein OR high-density lipoprotein) OR SM Dyslipidemias OR SM HIV OR SM HIV infections OR (HIV OR hiv-1 OR hiv-2* OR

hiv1 OR hiv2 OR hiv infect* OR "human immunodeficiency virus" OR "human immune deficiency virus" OR "human immuno-deficiency virus" OR "human immune-deficiency virus" OR "acquired immunodeficiency syndromes" OR "acquired immune deficiency syndrome" OR "acquired immuno-deficiency syndrome" OR "acquired immune-deficiency syndrome" OR HIV/AIDS) OR (tuberculosis OR tuberculoses OR tb) OR SM tuberculosis OR ("noncommunicable disease" OR "noncommunicable diseases" OR "non-communicable disease" OR "non-communicable diseases" OR NCD OR NCDs) OR SM "noncommunicable diseases" OR (comorbid* OR co-morbid* OR "co morbidity" OR multimorbidity OR multi-morbid OR "multi morbidity") OR SM multimorbidity OR SM comorbidity

S3 (multi-disease* OR multidisease* OR multi disease* OR multiple condition* OR multi-condition* OR multi condition* OR multiple illness* OR multi-illness* OR multi illness* OR multiple syndrome* OR multi-syndrome* OR multi syndrome* OR concurrent condition* OR concurrent illness* OR concurrent disease* OR co-existing disease* OR coexisting disease* OR co-existing illness* OR coexisting illness* OR co-existing syndrome* OR coexisting syndrome* OR co-existing condition* OR coexisting condition* OR co-occurring disease* OR co occuring disease* OR cooccuring disease* OR co-occurring illness* OR co occurring illness* OR cooccurring illness* OR co-occurring syndrome* OR co occurring syndrome* OR cooccurring syndrome* OR co-occurring condition* OR co occurring condition* OR cooccurring condition*) OR (chronic disease* OR lifestyle disease* OR "diseases of lifestyle" OR "disease of lifestyle") OR SM "Multiple Chronic Conditions" OR SM "Chronic Disease"

S4 S2 OR S3

S5 AB "Delivery of Health Care, Integrated" OR AB "Comprehensive Health Care" OR AB "Continuity of Patient Care" OR AB "Patient-Centered Care"

S6 ((“delivery of care” OR “delivery of health” OR "delivery of healthcare" OR "comprehensive healthcare" OR "comprehensive care" OR "comprehensive health" OR "continuity of patient care" OR "continuity of care" OR "continuity of health" OR "continuity of healthcare" OR "patient centered care" OR "patient centred care") OR ((referral AND consultation)) OR SM ("Referral and Consultation") OR (integrat* care OR "integration of care" OR integrat* services OR "integration of services" OR integrat* programmes OR integrat* programs OR “integration of programmes” OR “integration of programs” OR integrat* service delivery OR “integration of service delivery” OR integrat* services OR “integration of services” OR integrat* delivery OR integrat* management OR “integration of management”) OR (coordinat* care OR "coordination of care" OR coordinat* services OR "coordination of services" OR coordinat* programmes OR coordinat* programs OR “coordination of programmes” OR “coordination of programs” OR coordinat* service delivery OR “coordination of service delivery” OR coordinat* services OR “coordination of services” OR coordinat* delivery OR coordinat* management OR “coordination of management”) OR (co-ordinat* care OR "co-ordination of care" OR co-ordinat* services OR "co-ordination of services" OR co-ordinat* programmes OR co-ordinat* programs OR “co-ordination of programmes” OR “co-ordination of programs” OR co-ordinat* service delivery OR “co-ordination of service delivery” OR co-ordinat* services OR “co-ordination of services” OR co-ordinat* delivery OR co-ordinat* management OR “co-ordination of management”) OR (horizontal care OR vertical care OR horizontal services OR vertical services OR horizontal programmes OR horizontal programs OR vertical programmes OR vertical programs OR horizontal service delivery OR vertical service delivery OR horizontal services OR vertical services OR horizontal delivery OR vertical management OR vertical management) OR ((“multi team” OR multiteam “multi care” OR multicare OR “multi clinic” OR multiclinic OR “multi service” OR multiservice OR “multi program” OR multiprogram OR “multi programme” OR “multi delivery” OR multidelivery OR “multi management”)

S7 S5 OR S6

S8 "(developing country" OR "gross domestic" OR "gross national" OR "low income" OR "low-income" OR "middle income" OR "middle-income" OR LMIC OR LMICs OR "transitional country" OR "transitional countries" OR "third world" OR "lami country" OR "lami countries" OR "under developed" OR underdeveloped OR under-developed) OR ("low- and middle-income") OR ("low and middle income")"

S9 S1 AND S4 AND S7 AND S8

7. LILACS

(Words: hypertension OR "high blood pressure" OR systolic OR diastolic OR diabetes) AND

(Words: dyslipidemia OR cholesterol OR HIV OR tuberculosis OR multimorbidity OR comorbidity OR non-communicable disease) AND

(Words: LMIC OR low income OR middle income OR low-income OR middle-income OR developing country OR developing countries)

Supplementary file 2: List of excluded studies and reasons for exclusion

Studies excluded for wrong population	Studies excluded for wrong study design	Studies excluded for wrong intervention
Abrahams-Gessel 2018[1]	Ajay 2016[9]	Bachmann 2018[28]
Adomaviciute 2014[2]	Al Asmary 2013[10]	Hong 2013[29]
Alharbi 2014[3]	Garrib 2018[11]	Kowalski 2017[30]
Miao 2016[4]	Germe 2017[12]	McKee 2011[31]
Myers 2018[5]	Kwarisiima 2019[13]	Mendis 2010[32]
Rakic 2011[6]	Li 2013[14]	Pibernik-Okanovic 2015[33]
Sarrafzadegan 2006[7]	Mahomed 2014[15]	Saleh 2018[34]
Spaak 2017[8]	Narayanan 2012[16]	Sarrafzadegan 2009[35]
	Nigatu 2012[17]	Tourkmani 2018[36]
	Nyabera 2011[18]	Wenxi 2017[37]
	Patel 2018[19]	
	Patel 2015[20]	
	Rabkin 2018[21]	
	Samb 2010[22]	
	Sarraf-Zadegan 2003[23]	
	Sushilkumar 2015[24]	
	Tedjokusumo 2003[25]	
	Tiam 2012[26]	
	Wasay 2009[27]	

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Supplementary file 3: Summary of interventions according to the TIDiER checklist: Integrated models of care

Study ID	Ameh 2017		Rawat 2018*	Havlir 2019	
Intervention groups	**Intervention**	**Control**	**Intervention**	**Intervention**	**Control**
Name of intervention	Integrated chronic disease management (ICDM) model	Standard care in clinics where ICDM model was not piloted	Implementation of national policy to integrate HIV care into all PHC facilities	Integrated care: Baseline HIV and multi-disease testing plus annual testing, universal ART and patient-centered care	Usual care: Baseline HIV and multi-disease testing and national guideline-restricted ART, hypertension and diabetes care as per country standard of care
Aim of the intervention	To improve management of patients with HIV, TB, hypertension, diabetes, COPD, asthma, epilepsy and mental health conditions at PHCs	Not reported	To provide comprehensive HIV care (prevention, diagnosis, treatment initiation and follow-up) at PHC facilities	To remove patient-level barriers and maximise the efficiency of the health system To overcome barriers of universal access to HIV treatment and to be able to reach UNAIDS goals	Not reported
Physical and informational materials used	Not reported	Not reported	Not reported	Treatment guidelines ART tablets SMS reminders	National treatment guidelines
Procedures, activities and processes used in the intervention	Facility reorganisation: designated chronic care area; supply of critical medicines; pre-packaging of medication	Not reported	Policy to integrate HIV care into PHC clinics Training of nurses in comprehensive management of HIV: Nurse initiated	Community health campaigns (CHCs): Multi-disease testing for HIV, diabetes and hypertension; counselling and clinic appointments for participants with	Community health campaigns: Multi-disease testing for HIV, diabetes and hypertension; counselling and clinic appointments for participants with positive

	Clinical management support: use of guidelines to manage chronic diseases (PC101); human resources audit; capacity building; appropriate referral Ward-based outreach teams to ensure individual responsibility and "assisted" self-management Health promotion and population screening		Management of ART (NIMART) Training of nurses through the Practical Approach to Lung Health in South Africa (PALSA PLUS) Additional staff to strengthen drug delivery systems	positive tests; HIV positive participants received blood tests (CD4, t-cell count, HIV/RNA levels) and one-time round trip transportation voucher for first clinic visit Home-based testing for participants that did not attend CHCs Linkage to ART: HIV positive participants not on ART received appointments to initiate ART within a maximum of 7 days; clinic staff introduced themselves in person or by mobile phone; participants could contact hotline via phone or text message for questions or support; phone/SMS reminders about clinic visits Patient-centered care for HIV, diabetes, hypertension: 3-month visit intervals; flexible clinic hours; reduced waiting time at clinics;	tests; HIV positive participants received blood tests (CD4, t-cell count, HIV/RNA levels) and one-time round trip transportation voucher for first clinic visit ART, diabetes and hypertension treatment: provided in accordance with national guidelines

				welcoming staff; ART to all HIV positive participants; if not eligible for ART according to national guidelines, trial provided Truvada; hypertension and diabetes treated according to standard algorithms	
Who provided the intervention	Nurses	Nurses	Nurses	CHCs: Study team in collaboration with the local health units and the Ministry of Health in Uganda and Kenya Patient-centered care: government clinics augmented by trial staff	CHCs: Study team in collaboration with the local health units and the Ministry of Health in Uganda and Kenya Care in clinics: Clinic staff, augmented by additional staff funded by trial to mitigate staff shortages
Modes of delivery	Not reported	Not reported	Practical implementation of policy varied across clinics: Either disease-specific nurses in separate consulting rooms (co-location), or one nurse that provided comprehensive care for all diseases in single consultation room	Face-to-face, via telephone or text message	Face-to-face

Location of the intervention	Primary healthcare facilities	Primary healthcare facilities	Primary healthcare clinics: 37 urban clinics 65 rural clinics 30 clinics from former homeland	CHCs: Under large tents in all communities, or home-based Patient-centered care: At clinics	CHC: Under large tents in all communities, or home-based ART, diabetes, hypertension care: At clinics
When and how much the intervention was delivered	Unstable HIV and hypertension patients: follow-up every month Stable HIV and hypertension patients: follow=up every 2-3 months Routine referral of all patients to doctor: Every 6 months	Not reported	Not reported	CHCs: lasted 2 weeks at baseline, annually and at 3 year endpoint during weekdays, evenings and weekends Clinic visits: 3-month intervals	CHCs: lasted 2 weeks at baseline and at 3 year endpoint during weekdays, evenings and weekends Clinic visits: not reported
Tailoring of the intervention	Not reported	Not reported	Modular structures and pharmacy renovations to address space concerns in some clinics	Not reported	Not reported
Modifications of the intervention	Not reported	Not reported	Not reported	The end point of the trial was reduced from 5 years to 3 years	Control clinics implemented ART guidelines that were specific to Uganda and Kenya; during the trial, the threshold for eligibility for ART in these countries expanded from a specific CD4+ T-cell count (ranging from <350

					to <500) to universal treatment (regardless of CD4+ T-cell count)
Assessment of intervention adherence/fidelity	Not reported	Not reported	Not reported	Not reported	Not reported
Intervention delivered as planned	Not reported	Not reported	Not reported	Not reported	Not reported

*No control intervention described

HIV human immunodeficiency virus, TB tuberculosis, COPD chronic obstructive pulmonary disease, PHC primary healthcare clinics

Supplementary file 4: Summary of interventions according to the TIDiER checklist: Interventions to promote integrated management of care

Study ID	**Fairall 2016**		**Prabhakaran 2018**	
Intervention groups	**Intervention**	**Control**	**Intervention**	**Control**
Name of intervention	Primary Care (PC) 101	Usual care in for non-communicable and communicable diseases: Practical Approach to Lung Health and HIV/AIDS in South Africa (PALSA PLUS)	mWellcare	Enhanced usual care
Aim of the intervention	To provide comprehensive care for all symptoms, including NCDs, HIV, TB, mental health conditions, women's health	To provide a user-friendly management tool that integrates and harmonises disease-specific guidelines and presents them in a simple format, aligned with patient presentation in primary health care settings, expanded nurses' scope of practice and prescribing (not covering all NCDs)	To facilitate integrated management of hypertension, diabetes, comorbid depression, and alcohol and tobacco use	Not reported
Physical and informational materials used	PC 101 guideline: a 101-page clinical management tool in form of a ring-bound, colour illustrated booklet Desk pads with key messages for priority conditions to facilitate	Latest version (2011/2012) of PALSA PLUS: clinical management tool	mWellcare system: m-Health-based electronic decision-support system that generates recommendations based on patient profile and risk level used on Android tablet	Nurses received a tablet to collect baseline data (without the mWellcare system) Visible charts on the management of the conditions

	booking of follow-up appointments		Visible charts on the management of the conditions Pamphlets containing lifestyle advice	Pamphlets containing lifestyle advice
Procedures, activities and processes used in the intervention	Training of facility trainers Educational outreach sessions by facility trainers Expanded prescribing provisions for nurses Letters and SMS reminders of follow-up visits Financial compensation for patients (voucher for local grocery store) for travel costs and time	Training of facility trainers Educational outreach sessions by facility trainers Financial compensation for patients (voucher for local grocery store) for travel costs and time	Training of physicians on current clinical management guidelines and orientation to mWellcare system Training of nurses in management of hypertension, diabetes, depression, and tobacco and alcohol use Onsite supervision and support SMS reminders of follow-up visits and medication adherence	Training of physicians on clinical management guidelines for hypertension and diabetes Training of NCD nurses in management of hypertension and diabetes mellitus
Who provided the intervention	Training of facility trainers: Experienced adult education practitioner with a background in nursing, family physician who lead the expansion of the clinical management tool Educational outreach sessions: Nurse trainers	Training of facility trainers: not reported Educational outreach sessions: Nurse trainers Care: Nurses	Training: Study authors Care: NCD nurses and physicians	Training: Study authors Care: NCD nurses and physicians

	Care: Nurses			
Modes of delivery	Training and educational outreach sessions: face-to-face Care: Using PC 101 to guide management, details not reported	Training and educational outreach sessions: face-to-face Care: Using PALSA PLUS to guide management, details not reported	All training: face-to-face Care: Patient baseline data entered into mWellcare system which generated a decision support recommendation, lifestyle advice and suggested date for follow-up (printout). The recommendation was reviewed by the physician. Any changes to the recommended plan we captured in the mWellcare system. The nurse provided lifestyle advice and pamphlets	All training: face-to-face Care: According to clinical judgement of physician. Nurses provided and explained pamphlets on lifestyle advice
Location of the intervention	In primary healthcare clinics	In primary healthcare clinics	Community Health Centres	Community Health Centres
When and how much the intervention was delivered	Training of facility trainers: 5-days, in May 2011 and quarterly 1-day workshops Educational outreach sessions: Total of 155 educational outreach sessions, 8 sessions lasting 90 minutes at each of the 19 intervention clinics Care: Stable patients are seen by the nurse every 3-6 months	Educational outreach sessions: 90 minute sessions Follow-up sessions every year Distribution of updated tool every year Care: Stable patients are seen by the nurse every 3-6 months	Training for nurses using the mWellcare system: 3 days Onsite supervision: 2 days Care: follow-up visits according to the recommendation provided by the mWellcare system	Not reported Care: follow-up visits according to the discretion of the physician

Tailoring of the intervention	Not reported	Not reported	Not reported	Not reported
Modifications of the intervention	Unexpected co-intervention by the district department of health: "Chronic Disease Season" (3 month campaign), to improve NCD recognition and care, focusing on diabetes and hypertension, at clinic and community-level. In the community, free screening of blood pressure and glucose levels were offered in public spaces such as shopping centres. People with high values were referred to the clinic. Training of 33 community health workers to provide basic education on diet and lifestyle Facilitated group session to resolve tensions between nurses, doctors and pharmacists related to expanded prescribing provisions	Unexpected co-intervention by the district department of health: "Chronic Disease Season" (3 month campaign), to improve NCD recognition and care, focusing on diabetes and hypertension, at clinic and community-level. In the community, free screening of blood pressure and glucose levels were offered in public spaces such as shopping centres. People with high values were referred to the clinic. Training of 33 community health workers to provide basic education on diet and lifestyle	None reported	None reported
Assessment of intervention adherence/fidelity	Nurse trainers were observed during 5-day workshop and quarterly 1-day workshops Two nurse trainers were interviewed and focus group discussions were held in four	Not reported	Monthly visits to all sites by field coordinators who complete a checklist on: intervention delivery, source documents examination, protocol	Monthly visits to all sites by field coordinators who complete a checklist on: intervention delivery, source documents examination, protocol

	intervention clinics in December 2011		adherence and recording of adverse events Site visits by investigators: to monitor enrolment process, intervention delivery and protocol adherence	adherence and recording of adverse events Site visits by investigators: to monitor enrolment process, intervention delivery and protocol adherence
Intervention delivered as planned	Good uptake of nurse trainers, who completed all outreach sessions, and repeated some sessions to ensure that most staff could attend Due to absenteeism and shifts, not all nurses attended all the outreach sessions. In total, 18 nurses attended a median of six training sessions, five pharmacists and four doctors were trained Some variations in the uptake of the PC 101 tool were observed	By 2011, 70% of nurses working in the relevant districts had received training in PALSA PLUS.	Not reported	Not reported

Supplementary file 5: Risk of bias assessments for included studies

Prabhakaran 2018

Domain	Risk of bias	Support for judgement
Random sequence generation *(selection bias)*	**Low risk**	"An independent biostatistician performed central computer-based randomization of CHCs stratified by states (Haryana and Karnataka) and within each state by the availability of NCD nurses recruited under NPCDCS." "using block randomisation (with a block size of 2)"
Allocation concealment *(selection bias)*	**Low risk**	Unit of allocation was an institution. Allocation performed on all units at the start of the study.
Baseline outcome measurements similar	**Low risk**	Measurement of outcomes was conducted in a standardised way. Outcomes were pre-defined and subjective
Baseline characteristics similar	**Low risk**	The EUC arm had a higher proportion of participants with peripheral vascular disease (4.4% versus 0.3%), self-reported tobacco use (17.5% versus 10.0%) and alcohol use (12.3% versus 7.8%), and higher mean SBP (157.0 mm Hg versus 152.5 mm Hg). Outcome measures adjusted for relevant baseline characteristics.
Incomplete outcome data	**Low risk**	No incomplete outcome data suspected. Number of participants in whom the outcomes were assessed were mentioned in a general manner.
Blinding of participants and personnel *(performance bias)*	**High risk**	**Outcome group: All/** "Given the nature of the cluster-randomized trial design, neither personnel nor participants were blinded to the intervention."
Blinding of outcome assessment *(detection bias)*	**Unclear**	**Outcome group: All/** "Assessments at study end were carried out by independent outcome assessors" "It was difficult to blind independent assessors who carried out the end-of-study evaluations"
Protection against contamination	**Low risk**	**Outcome group: All/** low possibility of contamination across clusters
Selective Outcome reporting	**Low risk**	Data on cost-effectiveness mentioned in protocol but not reported in full report of the study, because primary outcome do not differ substantially, otherwise all primary and secondary outcomes reported
Recruitment bias *(e.g. individuals are recruited to the trial after the clusters have been randomized)*	**Unclear**	Patients were recruited after randomisation. Of eligible participants, n=165 in the intervention group and n=193 in the control group were not enrolled in the trial.
Baseline differences clusters	**Unclear**	Characteristics of cluster not described
Loss of clusters	**Low risk**	No loss of clusters reported
Incorrect analysis	Low **risk**	Adjusted for clustering
Comparability *(with RCTs randomised by individuals)*	**Low risk**	No similar studies randomised by individuals found in our search.

Fairall 2016

Domain	Risk of bias	Support for judgement
Random sequence generation *(selection bias)*	**Low risk**	"Randomisation was completed by the trial statistician using nQuery Advisor after recruitment of clinics, independently of the managers giving permission for the clinics to be included in the trial, and prior to patient recruitment and implementation of the intervention."
Allocation concealment *(selection bias)*	**Low risk**	Unit of allocation was an institution. Allocation performed on all units at the start of the study. "Randomisation was completed by the trial statistician using nQuery Advisor after recruitment of clinics, independently of the managers giving permission for the clinics to be included in the trial, and prior to patient recruitment and implementation of the intervention"
Baseline outcome measurements similar	**Low risk**	No differences between groups reported: Baseline BP and HbA1C similar
Baseline characteristics similar	**Unclear**	Baseline characteristics seem similar, but no statistical tests reported
Incomplete outcome data	**Low risk**	Loss to follow-up similar across groups and less than 20%
Blinding of participants and personnel *(performance bias)*	**High risk**	**Outcome group: All** **"Blinding of the intervention was not possible at the clinic level due to the nature of the intervention"**
Blinding of outcome assessment *(detection bias)*	**Unclear**	**Outcome group: All** No blinding of outcome assessors reported Outcome assessors not blinded. This might have influenced BP readings, but not HbA1C (blood test)
Protection against contamination	**Unclear**	**Outcome group: All** Contamination of study arms unlikely. Control clinics might have had access to the guidelines although cluster randomisation took place
Selective Outcome reporting	**Low risk**	**No selective outcome reporting suspected, all** outcomes **listed in the methods section are also** reported **in the results section** – All pre-specified outcomes listed in the trial registration record reported on
Recruitment bias	**Low risk**	"Randomisation was completed by the trial statistician using nQuery Advisor after recruitment of clinics, independently of the managers giving permission for the clinics to be included in the trial, and prior to patient recruitment and implementation of the intervention" All patients were enrolled after the clusters were randomised. However, all eligible patients were included in the study.
Baseline differences (clusters)	**Low risk**	Control clinics had more nurses per clinic and more pharmacies on site compared to the intervention group, but patient load was also higher in the control clinics. Ratio of nurses to patients was similar in both groups
Loss of clusters	**Low risk**	All clinics completed the trial
Incorrect analysis	**Low risk**	Analysis conducted on individual level, but results adjusted for cluster effects. "The cluster randomisation design was accounted for using robust cluster variance-covariance estimates."
Compatibility *(with RCTs randomised by individuals)*	**Low risk**	No similar studies randomised by individuals found in our search
Other bias	**Unclear**	"Midway through the trial, the district health department launched a 3-mo campaign called Chronic Disease Season in all clinics to improve NCD recognition and care. Chronic Disease Season focused on hypertension and diabetes and involved both community and clinic health workers. The community-level interventions included several [a]health screening days[o] in which free blood pressure and finger-prick glucose measurements were offered at venues such as shopping centres and town halls" (Page 7, end)

Havlir 2019

Domain	Risk of bias	Support for judgement
Random sequence generation (selection bias)	**Low risk**	Adequate method – mix of methods used, including computer generated, coin tossing and drawing of lots See description in protocol (p45 version 2.0 (Nov 2012)
Allocation concealment (selection bias)	**Low risk**	Communities were matched and randomised within each pair. Method adequate to not be able to predict allocation
Baseline outcome measurements similar	**Unclear**	No baseline outcome measurements for HIV and hypertension control Page 25, online supplement to article
Baseline characteristics similar	**Low risk**	No obvious difference observed
Incomplete outcome data	**Unclear**	Unclear for HIV and Hypertension cohort, not clear how many at baseline.
Blinding of participants and personnel (performance bias)	**High risk**	No blinding of participants and personnel due to the nature of the intervention. Can influence behaviour of both participants and personnel
Blinding of outcome assessment (detection bias)	**Unclear**	Not reported
Protection against contamination	**Unclear**	Distance from other potential trial communities taken into consideration as part of the eligibility criteria. Migration in and out of communities
Selective Outcome reporting	**Unclear**	Not clear whether dual control of HIV and Hypertension/NCDS was pre-specified
Recruitment bias	**Low risk**	Communities were recruited (selected) before randomisation. Participants were recruited after randomisation, but a household census and Community health campaigns to reach most people in community
Baseline differences (clusters)	**Unclear**	No description of clusters, but cluster pairs were matched for randomisation
Loss of clusters	**Low risk**	No loss of clusters
Incorrect analysis	**Unclear**	Not clear whether adequately adjusted for clustering
Compatibility (with RCTs randomised by individuals)	**Low risk**	No similar studies using individual randomisation found in our search
Other bias	**Unclear**	Primary endpoint should have been 5-year cumulative HIV incidence, but this was shortened to 3 years as the WHO recommendation on ART therapy changed

Rawat 2018

Domain	Risk of bias	Support for judgement
Intervention was independent of other changes	**Low risk**	No other intervention identified. Also, clinics were excluded if they were identified as 'priority sites' that were specifically designed to deliver ART.
The shape of the intervention effect was pre-specified	**High risk**	The shape of the intervention effect was not pre-specified.
The intervention was unlikely to affect data collections	**Low risk**	Data was collected from TIER.net (3 interlinked electronic registers) and the District Health Information System (DHIS) for data collected before and after the intervention.
Knowledge of the allocated intervention *(adequately prevented during the study)*	**Low risk**	Outcomes were based on indicators monitored by the Free State Department of Health. Methods of data collection were similar before and after the intervention, therefore the intervention did not affect data collection.
Incomplete outcome data was likely to bias results	**Unclear**	Post-intervention data for diabetes outcomes only available for 18 months post intervention. For other outcomes there is data for 30 months.
Outcomes were reported selectively	**Low risk**	All outcomes reported in the methods section were reported in the results section
Other risks of bias	**Low risk**	No other risks of bias identified. As integration took place at various intervals, seasonality assumed not to have an effect.

Ameh 2017

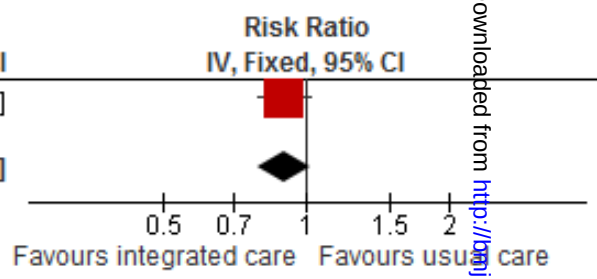
Domain	Risk of bias	Support for judgement
Intervention was independent of other changes	**Low risk**	No other changes reported.
The shape of the intervention effect was pre-specified	**Low risk**	Point of analysis is the point of intervention
The intervention was unlikely to affect data collections	**Unclear**	It can be assumed that the re-organisation of care delivery also affected data collection in the intervention facilities
Knowledge of the allocated intervention *(adequately prevented during the study)*	**Low risk**	Data was collected retrospectively from patient records. Patients were recruited in June 2013, and data collected from Jan 2011 to June 2013. Methods of data collection were similar before and after the intervention and the intervention did not affect data collection.
Incomplete outcome data was likely to bias results	**Low risk**	No incomplete outcome data suspected. No attrition or missing cases reported, only data for diabetes patients was not reported because there were too few cases (n=4)
Outcomes were reported selectively	**Low risk**	No selective outcome reporting suspected. All outcomes reported in the methods section are reported in the results section
Other risk of bias	**Low risk**	No other sources of bias identified

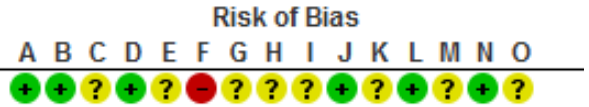
Supplementary file 6: Forest plots

Comparison 1: Integrated models of care vs. usual care
Outcome: Mortality

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
Havlir 2019	-0.1054	0.0665	100.0%	0.90 [0.79, 1.03]
Total (95% CI)			**100.0%**	**0.90 [0.79, 1.03]**

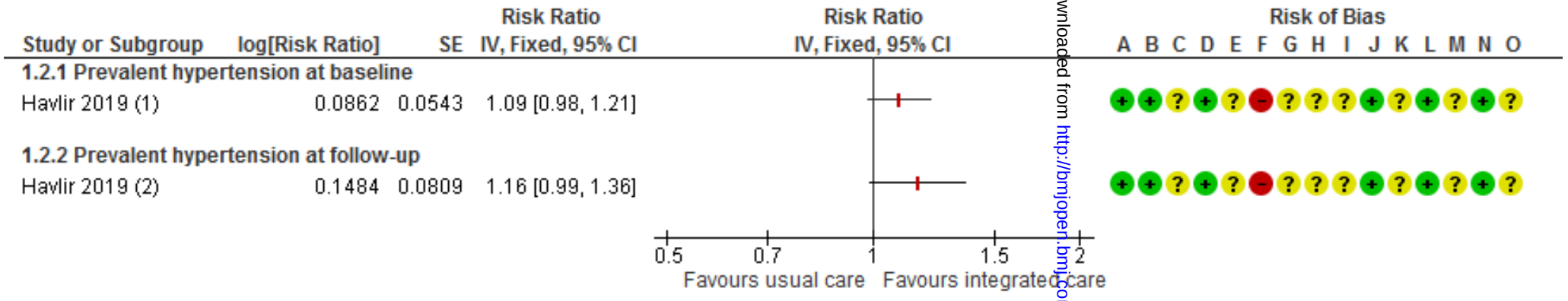
Heterogeneity: Not applicable
Test for overall effect: Z = 1.58 (P = 0.11)





Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Baseline outcome measurements similar
(D) Baseline characteristics similar
(E) Incomplete outcome data (attrition bias)
(F) Blinding of participants and personnel (performance bias)
(G) Blinding of outcome assessment (detection bias)
(H) Protection against contamination
(I) Selective reporting (reporting bias)
(J) Recruitment bias
(K) Baseline differences (clusters)
(L) Loss of clusters
(M) Incorrect analysis
(N) Compatibility with RCTs randomised by individuals
(O) Other bias

Comparison 1: Integrated models of care vs. usual care
Outcome: BP control



Footnotes

(1) Among people living with HIV (PLHIV)

(2) Among people living with HIV (PLHIV)

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Baseline outcome measurements similar

(D) Baseline characteristics similar

(E) Incomplete outcome data (attrition bias)

(F) Blinding of participants and personnel (performance bias)

(G) Blinding of outcome assessment (detection bias)

(H) Protection against contamination

(I) Selective reporting (reporting bias)

(J) Recruitment bias

(K) Baseline differences (clusters)

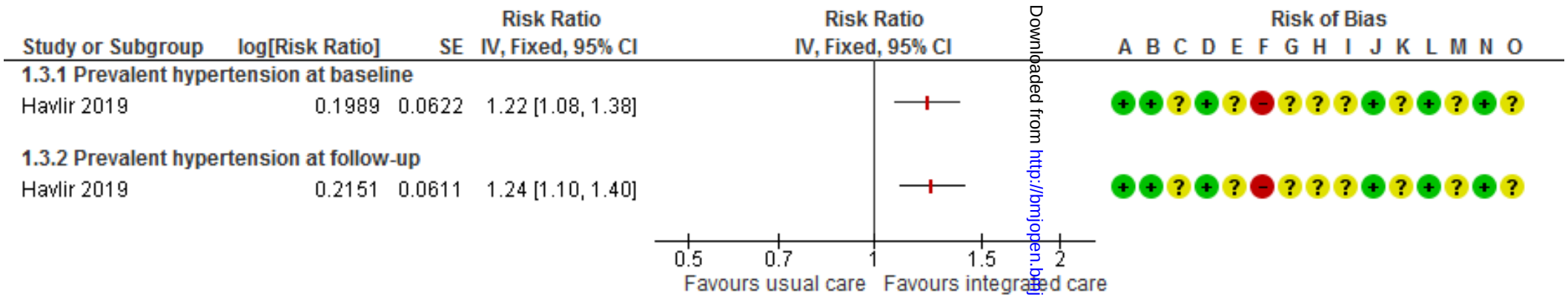
(L) Loss of clusters

(M) Incorrect analysis

(N) Compatibility with RCTs randomised by individuals

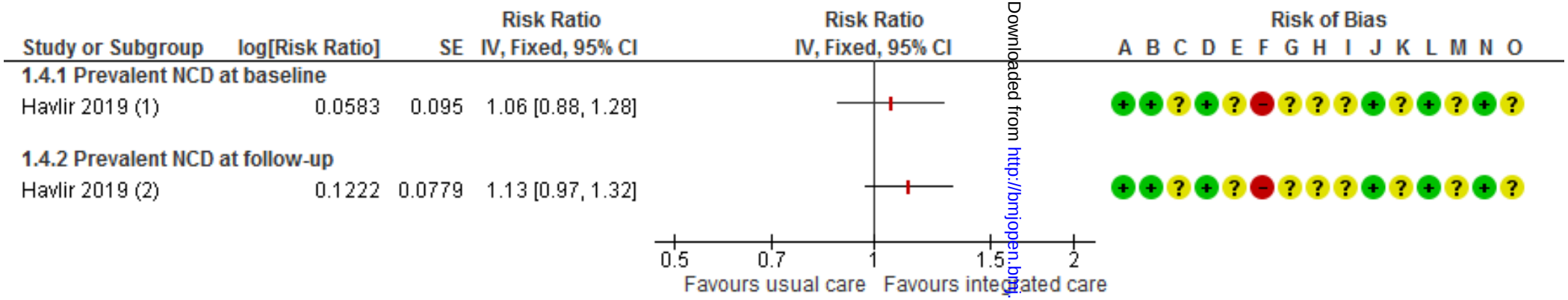
(O) Other bias

Comparison 1: Integrated models of care vs. usual care
Outcome: BP and HIV control



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Baseline outcome measurements similar
(D) Baseline characteristics similar
(E) Incomplete outcome data (attrition bias)
(F) Blinding of participants and personnel (performance bias)
(G) Blinding of outcome assessment (detection bias)
(H) Protection against contamination
(I) Selective reporting (reporting bias)
(J) Recruitment bias
(K) Baseline differences (clusters)
(L) Loss of clusters
(M) Incorrect analysis
(N) Compatibility with RCTs randomised by individuals
(O) Other bias

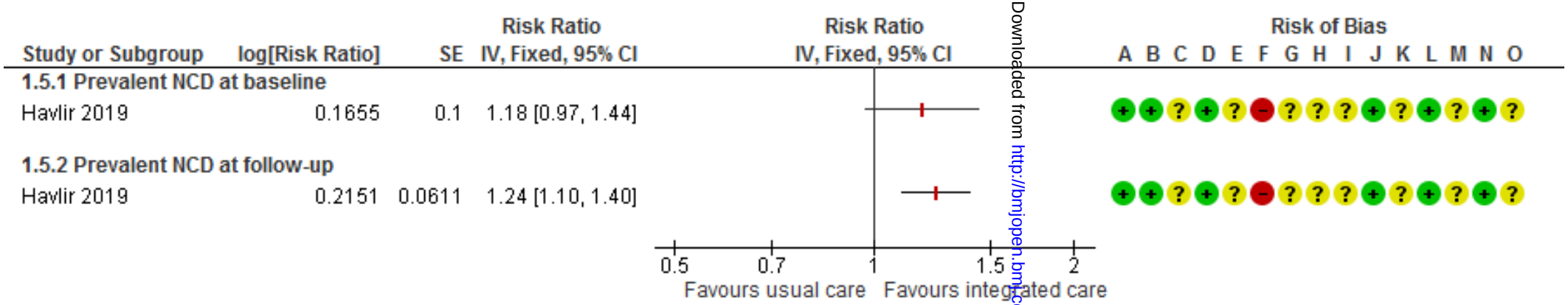
Comparison 1: Integrated models of care vs. usual care
Outcome: NCD control



Footnotes
(1) Among PLHIV
(2) Among PLHIV

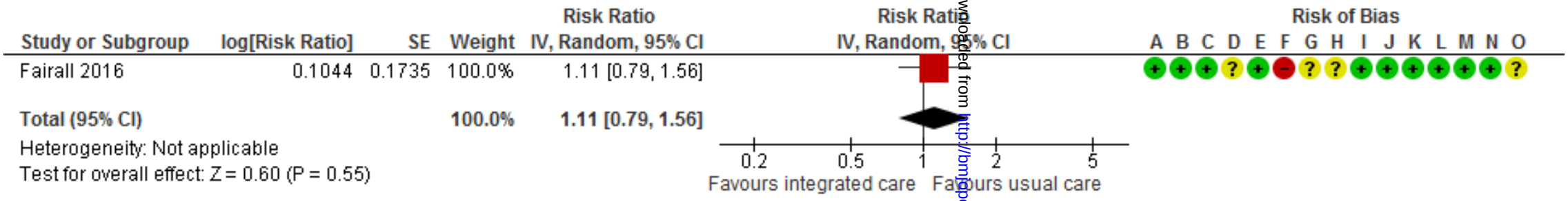
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Baseline outcome measurements similar
(D) Baseline characteristics similar
(E) Incomplete outcome data (attrition bias)
(F) Blinding of participants and personnel (performance bias)
(G) Blinding of outcome assessment (detection bias)
(H) Protection against contamination
(I) Selective reporting (reporting bias)
(J) Recruitment bias
(K) Baseline differences (clusters)
(L) Loss of clusters
(M) Incorrect analysis
(N) Compatibility with RCTs randomised by individuals
(O) Other bias

Comparison 1: Integrated models of care vs. usual care
Outcome: NCD and HIV control



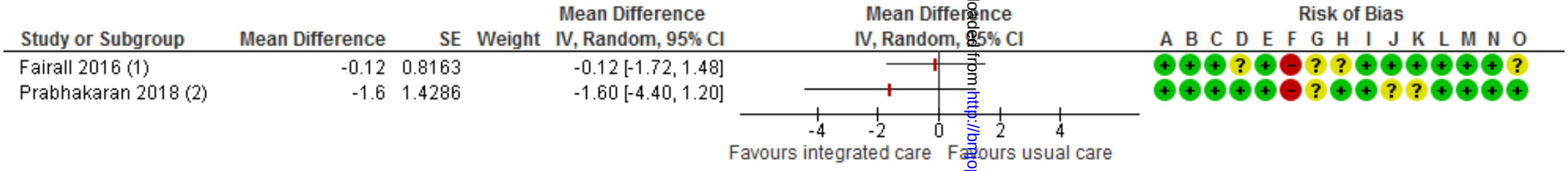
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Baseline outcome measurements similar
(D) Baseline characteristics similar
(E) Incomplete outcome data (attrition bias)
(F) Blinding of participants and personnel (performance bias)
(G) Blinding of outcome assessment (detection bias)
(H) Protection against contamination
(I) Selective reporting (reporting bias)
(J) Recruitment bias
(K) Baseline differences (clusters)
(L) Loss of clusters
(M) Incorrect analysis
(N) Compatibility with RCTs randomised by individuals
(O) Other bias

Comparison 2: Strategies to promote integrated models of care vs. usual care
Outcome: Mortality



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Baseline outcome measurements similar
(D) Baseline characteristics similar
(E) Incomplete outcome data (attrition bias)
(F) Blinding of participants and personnel (performance bias)
(G) Blinding of outcome assessment (detection bias)
(H) Protection against contamination
(I) Selective reporting (reporting bias)
(J) Recruitment bias
(K) Baseline differences (clusters)
(L) Loss of clusters
(M) Incorrect analysis
(N) Compatibility with RCTs randomised by individuals
(O) Other bias

Comparison 2: Strategies to promote integrated models of care vs. usual care
Outcome: Depression



Footnotes

(1) Change from baseline to follow-up; 10-item Center for EpidemiologicStudies...

(2) Value at follow-up; Patient Health Questionnaire-9

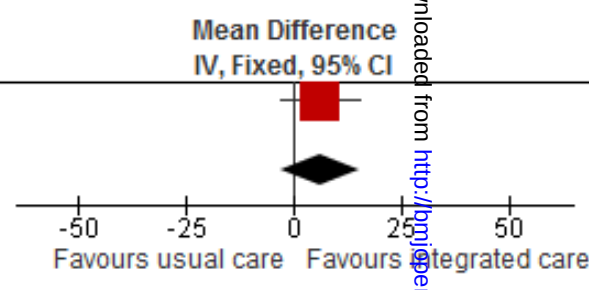
Risk of bias legend

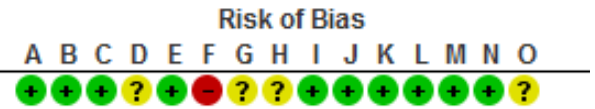
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Baseline outcome measurements similar
(D) Baseline characteristics similar
(E) Incomplete outcome data (attrition bias)
(F) Blinding of participants and personnel (performance bias)
(G) Blinding of outcome assessment (detection bias)
(H) Protection against contamination
(I) Selective reporting (reporting bias)
(J) Recruitment bias
(K) Baseline differences (clusters)
(L) Loss of clusters
(M) Incorrect analysis
(N) Compatibility with RCT of randomised by individuals
(O) Other bias

Comparison 2: Strategies to promote integrated models of care vs. usual care
Outcome: Quality of life

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Fairall 2016 (1)	6.06	4.7501	100.0%	6.06 [-3.25, 15.37]
Total (95% CI)			**100.0%**	**6.06 [-3.25, 15.37]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.28 (P = 0.20)





Footnotes
(1) Euro-Qol-5D visual analogue scale: 0=worst imaginable state of health,...

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Baseline outcome measurements similar
(D) Baseline characteristics similar
(E) Incomplete outcome data (attrition bias)
(F) Blinding of participants and personnel (performance bias)
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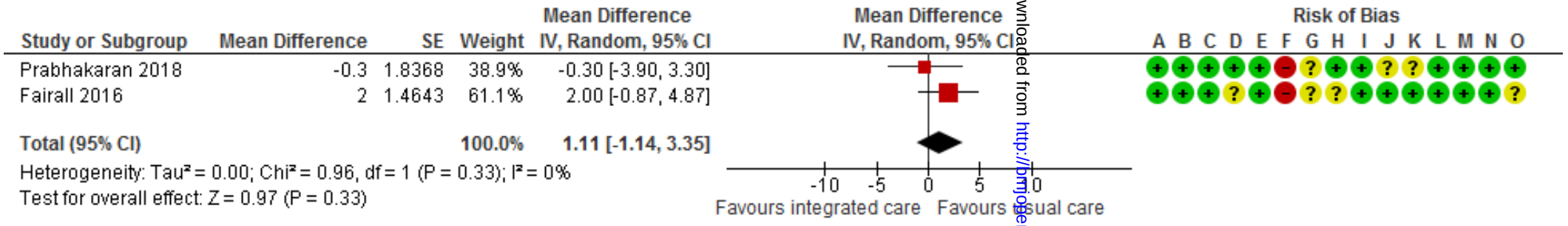
(K) Baseline differences (clusters)
(L) Loss of clusters
(M) Incorrect analysis
(N) Compatibility with RCTs randomised by individuals
(O) Other bias

Comparison 2: Strategies to promote integrated models of care vs. usual care
Outcome: Change in systolic BP



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Baseline outcome measurements similar
(D) Baseline characteristics similar
(E) Incomplete outcome data (attrition bias)
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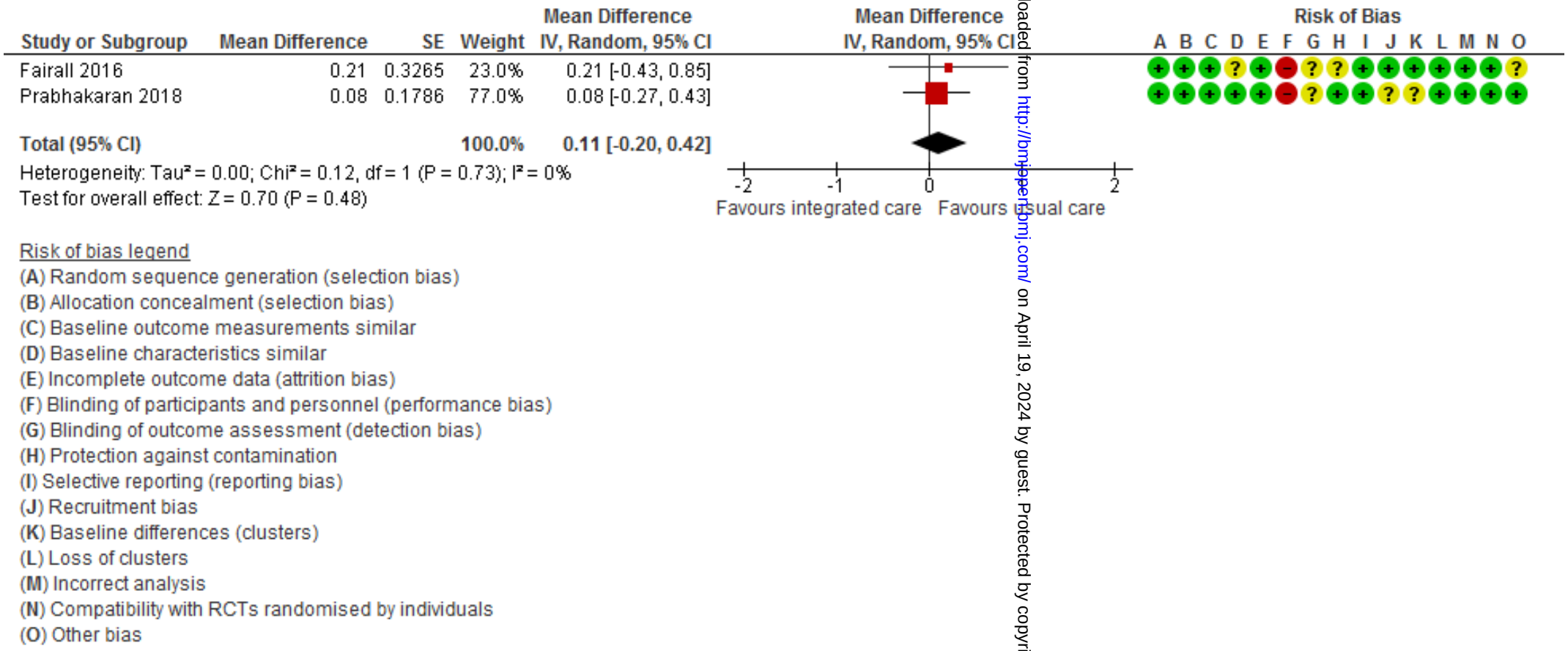
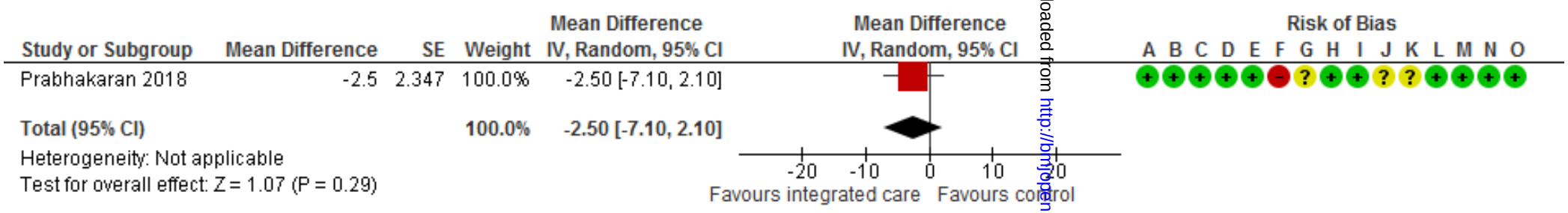
(J) Recruitment bias
(K) Baseline differences (clusters)
(L) Loss of clusters
(M) Incorrect analysis
(N) Compatibility with RCTs randomised by individuals
(O) Other bias

Comparison 2: Strategies to promote integrated models of care vs. usual care
Outcome: Change in HbA1c



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Baseline outcome measurements similar
(D) Baseline characteristics similar
(E) Incomplete outcome data (attrition bias)
(F) Blinding of participants and personnel (performance bias)
(G) Blinding of outcome assessment (detection bias)
(H) Protection against contamination
(I) Selective reporting (reporting bias)
(J) Recruitment bias
(K) Baseline differences (clusters)
(L) Loss of clusters
(M) Incorrect analysis
(N) Compatibility with RCTs randomised by individuals
(O) Other bias

Comparison 2: Strategies to promote integrated models of care vs. usual care
Outcome: Change in total cholesterol



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Baseline outcome measurements similar
(D) Baseline characteristics similar
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(L) Loss of clusters
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(O) Other bias

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary file 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6-7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7, Figure 2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-12, Supplementary files 3 and 4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13, Figure 3, 4 and supplementary file 5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Supplementary file 6
Synthesis of results	21	13-20	11-18
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 3 and 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	22

PRISMA 2009 Checklist

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

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