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What are the important design features of personal health records to improve medication adherence for patients with long term conditions? A systematic literature review.

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What are the important design features of personal health records to improve medication adherence for patients with long term conditions? A systematic literature review.

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Literature review

KEYWORDS

Personal health record, medication adherence, medical informatics, systematic literature review, long-term conditions

ABSTRACT

Objectives: This systematic literature review aims to identify important design features of the electronic personal health record (PHR) that may improve medication adherence in the adult population with long-term conditions and whether implementation factors or demographics interact with the PHR impact.

Data sources: PubMed (including MEDLINE), CINAHL, Science Direct (including EMBASE), BioMed Central, ACM digital, Emerald Insight, Google Scholar and Research Gate.

Methods: Studies published in the last fifteen years, in English, were included if the participants were adults, with at least one long-term condition, able to self-administer their medication and were treated in primary care settings. The quality of evidence was assessed with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system and the risk of bias was appraised using the Cochrane RevMan tool.

Results: From a total of 35 studies that matched the inclusion criteria, 12 were excluded due to low quality of evidence, 13 rated moderate and 10 high quality. All the included studies had low sample size and limited follow-up duration. The most frequently identified conditions were HIV and diabetes. The most common measure of medication adherence was the Morisky Medication Adherence Scale. This review did not identify any papers with negative results. It was not possible to numerically aggregate the PHR effect due to high heterogeneity of the medication adherence measurement, study type, participants and PHRs used. This review identified 12 PHR design features that seem to have an impact on medication adherence, but it was impossible to draw conclusions as to which feature is important to what group of patients and why.

Conclusion: Although we found recurrent evidence that PHRs can improve medication adherence, there is little evidence to date to indicate which design features facilitate this process.

Registration: PROSPERO CRD42017060542

ARTICLE SUMMARY

Strengths and limitations of this study

- This is a systematic literature review that follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines;
- The protocol was published before conducting the study to avoid data-driven decisions; no deviations from the protocol have been made;
- A comprehensive literature search was carried out using eight major research paper databases, hand-searching and snowballing;
- All included studies were quality assessed using well-cited tools and documentation;
- A study limitation is that only studies published in English language were included

Literature review

INTRODUCTION

NHS policy anticipates that increasing usage of health apps by patients will reduce demand on healthcare services. Current NHS policy documents and frameworks such as *Personalised Health and Care 2020* (PHC2020) [1] and the *Five Year Forward View* [2] advocate that information and communication technology (ICT) can reduce healthcare costs, improve healthcare outcomes and this can be achieved by 2020. This assertion, however, is not based upon scientific research, so the claimed benefits remain aspirational.

Currently, 74% of UK nationals older than 45 years old and almost all younger adults are using the internet almost every day.[3] Based on the results of a 2017 US survey, roughly 40% of chronically ill patients were interested in using technology to assist them with medication, diagnosis, test results and managing their condition in their home environment.[4]

A form of ICT that could potentially benefit the patients and the healthcare services is the electronic personal health records (PHR). A PHR has been defined as: "online systems that include collections of patients' healthcare and medical data, which utilise health informatics standards to enable patients to share, organize and manage these data according to their own views".[5] Some of the indicated benefits of PHRs are the ability of PHR to improve patient outcomes, decrease care cost, allow patients the ability to self-manage their health, increase access to care especially in remote areas, empower patients and improve medication adherence.[6,7]

Medication adherence is a well-known challenge in healthcare,[8,9] but there is limited evidence whether PHRs actually improve medication adherence in chronically ill adults and no evidence synthesis as to which PHR design features are the most effective. Medication adherence can be defined as "the extent to which a person's behaviour towards their medication intake, corresponds with agreed recommendations from a health care provider".[9] Based on the ABC taxonomy [10] for medication adherence, there are three components to medication adherence: initiation (the time until the first dose has been taken), implementation (the extend to whether a patient's dosage consumption correspond to the prescribed dose regimen) and discontinuation (stop taking the medication).[10]

This is the first systematic literature review that aims to identify important design features of the PHR that may improve medication adherence in the adult population with long-term conditions.

Objectives

Primary objective

Identify the important design features of the PHR that may improve medication adherence in the adult population with long-term conditions.

Secondary objectives

- Identify the PHR design features that improve medication adherence in the cases of:
  - polypharmacy;
  - specific long term condition groups;
- Identify if there is a correlation between participants' demographic characteristics, their usage of PHRs and their medication adherence;
- Explore how implementation factors affects medication adherence.

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METHODS

This systematic review is registered in the prospective register of systematic reviews (PROSPERO), registration number CRD42017060542 and follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[11] The PRISMA checklist is provided as an additional file. The protocol for this study is published.[5]

Study eligibility and selection

This review's inclusion and exclusion criteria are illustrated in Table 1 and are detailed in the published protocol.[5] There have been no deviations from the protocol.

Table 1 Summary of the PICOS elements included and excluded in the systematic review

	Inclusion criteria	Exclusion criteria
Participants		
	Humans Adults with at least one long term condition Patients that can self-administer their medication Patients that are able to communicate freely and able to self-manage their medication. Patients treated outside the hospital only	Animals Pregnant, cancer or terminally ill patients Adults with medically serious problems that are not classified as long term conditions Patients that require assistance with taking their medication Patients unable to communicate or unable to self-manage their medication. Inpatients or patients living in care homes
Intervention		
	Interventions of any type, intensity and frequency, that aim to investigate the effect of electronic PHRs in medication adherence, concordance, compliance or persistence.	N/A
Comparators		
	Non-PHR	No comparison has been made with no-PHR or with usual care
Outcome		
	Any outcome related to the effect of electronic PHRs in medication adherence, concordance, compliance or persistence.	N/A
Study design/type		
	Studies or literature reviews published in the last fifteen years, without any geographical restriction.	Abstract-only reports without any references, commercial studies, party political statements, general discussion papers, magazine or newspaper articles, withdrawn abstracts or articles, protocols of reviews.

Literature review

Literature search

Mendeley software was used as the bibliographic software. One author (EA) scanned the titles and abstracts and excluded studies that clearly did not meet the inclusion criteria. Full-text versions of the remaining articles were obtained and screened by the same author, using the criteria listed on Table 1. All the excluded studies were listed with at least one reason for exclusion. In case of uncertainty, the author PS was advised and there was a discussion until an agreement was made. The reference lists of the included studies were examined to identify additional relevant literature. A hand-search of JMIR Medical Informatics, BMC Medical Informatics and Decision Making and BMJ Open was conducted by EA to identify further literature, as they were the three high impact factor, most cited journals in the search we have done that far.

Data extraction and analysis

EA extracted the data in the predefined data extraction forms.[5] The narrative analysis of the generated data was performed by EA author and validated by PS.[5]

Quality assessment

The quality of all included studies was assessed by the first author (EA) and 25% of the included studies were assessed by the second author (PS). The Joanna Briggs Institute (JBI) critical appraisal questionnaires were used to implement the GRADE approach [12] of quality assessment of the included studies. The GRADE approach is proposed by the Cochrane Collaboration and it favours the JBI critical appraisal tools.[13]

The final quality scores per paper (Table 2) were assigned based upon five factors: risk of bias,[14] inconsistency,[15] indirectness,[16] imprecision [17] and publication bias.[18] All the studies were graded based on their study type, for example RCTs and systematic literature reviews started as high quality studies. Using the GRADE categories we started from the highest possible score based on the study's study type, using the JBI questions to extract data per paper for the GRADE scoring, reducing the quality for each instance of the factors mentioned above.

Risk of bias

The Cochrane Collaboration's tool for assessing risk of bias was used in terms of selection, performance, detection, attrition, reporting and other biases. The 'other' bias category incorporates risks of bias based on:

- Study population (experimental studies);
- Length of follow-up (experimental studies);
- Overall length of study (non-RCTs);
- Self-reported adherence (all studies);
- Reporting quality and quality of the included studies (reviews of the literature).

RESULTS

Literature search results

Error! Reference source not found. illustrates the literature search and selection method, presenting explanations for the exclusion of studies. Once duplicates were removed, a total of 1787 original works were identified and 23 were finally included in the qualitative synthesis.

Literature review

Characteristics of included studies

This review includes studies conducted in the USA (n=7), globally (n=7), and in Switzerland (n=2). Most studies had included participants, which have least one long term condition (n=9), diabetes (n= 5) and HIV (n=3). Most studies were published in 2014 (n=6), 2016 (n=4) and 2017 (n=4). The majority of the included studies (n = 18) reported a positive result in terms of the impact on medication adherence, with four studies identifying mixed results [19–22] and two studies found no difference.[23,24] No study identified negative results. Eight out of 10 high quality studies and nine out of 13 moderate quality studies found positive results with medication adherence. The main study characteristics are illustrated in Table 2.

Literature review

Table 2 Included Studies Characteristics

Study	Study type	Participants				Intervention	Control		Medication adherence assessment	Long Term Condition	Follow-up (months)	Medication adherence results	Quality
		Number	Mean Age	Male %	Education (>= high school %)	Name	Number	Type of Care					
Allam (2015)	RCT	155	57.96	54.1	76.1	ONESelf	40	Usual care	Prescription Opioid Misuse Index	Rheumatoid arthritis	4	Positive	Moderate
Chrischilles (2014)	RCT	1075	72.3	43.2	98.7	Iowa PHR	273	Usual care	Self-reported	At least one	12	No difference	Moderate
Dabbs (2016)	RCT	201	62	55.2	94	Pocket PATH	Not stated	Usual care	Health Habits Survey	Lung transplant recipients (LTRs)	12	Positive	High
Dorr (2007)	Systematic Literature Review	n/a	n/a	n/a	n/a	More than one	n/a	Usual care	n/a	At least one	n/a	Mixed	Moderate
Fioravanti (2015)	RCT	51	Not stated	Not stated	Not stated	More than one	25	Usual care	Self-reported	Diabetes (all types)	1	Positive	Moderate
Glaser (2017)	RCT	221	Not stated	58.4	72	Self	Not stated	Usual care	Lab results	At least one	9	Positive	High
Glasgow (2012)	RCT	332	61.4	95	86	My Path to Health Life	Not stated	Enhanced Usual care	Hill-Bone scale	Diabetes type 2	12	No difference	Moderate

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Grant (2008)	RCT	244	Not stated	51	Not stated	Not named	118	Usual care	Medication initiation or dosage adjustment	Diabetes type 2	12	Positive	High
Harrison (2014)	Systematic Literature Review	n/a	n/a	n/a	n/a	More than one	n/a	Usual care	n/a	Diabetes (all types)	n/a	Positive	Moderate
Lakshminarayana (2017)	RCT	201	60.3	60.7		Parkinson's Tracker	90	Usual care	MMAS-8	Parkinson's disease (PD)	4	Positive	Moderate
Luque (2012)	RCT	29	48	55	69	MyMedical	n/a	Usual care	Self-reported	HIV	2	Positive	Moderate
McDermott (2013)	Systematic Literature Review	n/a	n/a	n/a	n/a	More than one	Not stated	Usual care	n/a	At least one	n/a	Positive	High
McLean (2016)	Systematic Literature Review	n/a	n/a	n/a	n/a	More than one	Not stated	Usual care	n/a	Asthma	n/a	Mixed	High
Mira (2014)	RCT	99	71.9	55.5	Not stated	ALICE	48	Usual care	MMAS-4	At least one	11	Positive	Moderate
Mistry (2015)	Systematic Literature Review	n/a	n/a	n/a	n/a	More than one	n/a	Usual care	n/a	At least one	n/a	Positive	High

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Morton (2017)	Systematic Literature Review	n/a	n/a	n/a	n/a	More than one	n/a	Usual care	n/a	At least one	n/a	Positive	High
Park (2014)	Systematic Literature Review	n/a	n/a	n/a	n/a	More than one	n/a	Usual care	n/a	At least one	n/a	Mixed	High
Perera (2014)	RCT	28	46	93	Not stated	Not named	11	Usual care	MARS, pharmacy dispensing records, and lab tests	HIV	3	Positive	Moderate
Riva (2014)	RCT	51	47.5	49	76.4	ONESelf	24	Usual care	Prescription Medication Use and Perception of Risk Instrument	Chronic back pain (CBP)	5	Positive	High
Stephani (2016)	Systematic Literature Review	n/a	n/a	n/a	n/a	More than one	n/a	Usual care	n/a	At least one	n/a	Mixed	Moderate
Tang (2013)	RCT	415	53.7	60	94.3	Self	213	Usual care	diabetes control	Diabetes type 2	12	Positive	High
Westergaard (2017)	Qualitative	19	49.3	63	74	More than one	Not stated	Usual care	Self-reported	HIV	n/a	Positive	Moderate

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Zettl (2016)	Cohort Study	669	38.4	29	28	Self	330	Paper based PDA	Number of injections per study interval.	Multiple sclerosis (MS)	24	Positive	Moderate

Literature review

Primary objective

Table 3 presents the PHR design features that were identified in the literature and are the generated themes of this literature review. The definitions of the PHR design features derive from commercial PHRs that are implementing them or the wider literature regarding PHRs and personal experience, since there are no International Standards Organization (ISO) standards or universally accepted terminology.

Table 3 PHR design features

Feature	Definition	Medication adherence results by study		
		Positive	No difference	Mixed
Reminder	Reminders to take medication or to reorder their prescriptions, agnostic to the patient's chronic condition, demographics or any other external factor.	14	1	4
Education	Includes smaller features, like search bars and views, which can improve the user's health literacy and understanding of their condition.	6	2	1
Personalisation and tailoring	The personalisation involves presenting a health message specific to the individual patient's condition and demographic characteristics, whilst tailoring involves developing a PHR based on the individual's characteristics.[25]	11	1	-
Feedback and alerts	Medical emergency alerts in the form of a press button alert or SMS, such as the ones a user may find in the MyALERT PHR.[26]	13	2	3
Gamification	An umbrella term that includes the use of game design characteristics in non-game contexts.[27]	6	1	1
Medication management	Includes all the features that a chronically ill patient may need to conform to everyday life.[28]	14	2	3
Medical appointment management	Medically related appointment tracking, re-scheduling and arrangement.[29]	4	-	1
Diary and self-monitoring	A combination of features related to health or medication intake monitoring.[30]	11	2	4
Health condition management	Includes all the lab and medical tests results and integration of existing clinical data.[25]	2	1	1
Set goals	Includes all the elements that are necessary for setting and managing goals.	4	1	1
Patient's blog	Includes sharing in social media or blogging regarding health.[31]	2	-	-
Tethered	Are the PHRs which are connected with an electronic health record (EHR).[32]	4	-	-

All the PHR design features, which are constitute the themes derived from our thematic analysis,[33] are interlinked and overlap. NVivo 11 was used to cluster our codes into potentially more

comprehensive themes. The initial themes were clustered together based on coding similarity, which means that if there were coding many of the same included studies, they then were clustered together.

- reminder and medical appointment management (used in 5 studies)
- diary and self-monitoring (used in 17 studies)
- feedback and alerts and health condition management (used in 4 studies)
- medication management and patients blog (used in 2 studies)
- personalisation & tailoring (used in 12 studies)
- gamification (used in 8 studies)
- education and set goals (used in 6 studies)

Secondary objectives

PHR design features that improve medication adherence in case of polypharmacy

Even though multiple papers are including polypharmacy or multi-morbidity factors about their participants, they do not explore whether there is a correlation or an association between polypharmacy and the PHR usage or medication adherence improvement or not. There is a trend that the more medications a person uses the less a reminder helps, but this is not a conclusion directly supported by the data, but an argument emerging from multiple studies.[24,31,34,35]

PHR design features that improve medication adherence for specific long term condition groups

This research identified a number of chronic conditions. However, only diabetes and HIV can be used to analyse the impact that the PHR design features are having in medication adherence, since the rest of the conditions are included in just one study.

HIV

Three studies have been included that discuss how the use of PHRs affect medication adherence of adults with HIV.[35–37] All three studies produced positive results, having a very small (less than 50) number of participants that are also predominantly male and younger than 50 years old. Two studies are RCTs,[36,37] having follow-up duration of 2 to 3 months and the other one is a qualitative study [35] without any follow-up. All three studies include the personalisation and tailoring design feature, two of the studies use reminders, one study uses feedback and alerts and health condition management and one other study uses diary and self-monitoring design feature.

Diabetes

Five studies have been included that discuss how the use of PHRs affect medication adherence of adults with diabetes.[23,38–41] All studies found positive results regarding medication adherence, apart from Glasgow *et al.*[23] Four studies used diary and self-monitoring [23,38–40] or personalisation and tailoring,[23,38,40,41] three studies used education and set goals [23,38,40] or gamification [23,38,41] and one [40] used feedback and alerts and health condition management PHR design features. All studies were RCTs apart from Harrison *et al.*[39] The RCTs follow-up duration was 12 months apart from Fioravanti *et al*,[38] which was 1 month.

Association between participants' demographic characteristics, their usage of PHRs and their medication adherence

Data regarding patients' demographics and medication adherence were collected and analysed. This analysis excludes the 8 literature reviews, since it was impossible to collect accurate demographics from them. Only two [36,42] of the 15 studies provide a detailed description of the participants'

ethnicity. Two studies [43,44] are also providing data regarding the technology literacy of the participants and two other studies [23,36] provide data for the health literacy of the participants.

Twelve of the 15 studies provided age group details, which illustrate that the younger the participants, the more positive results regarding medication adherence were identified. This could be due to the presumed technological literacy of younger generations, however it was impossible to account for this confounding factor, since no data were supplied. Also the lower the number of participants in an experimental study (less than 251), the higher the impact of PHR in medication adherence. This could arguably illustrate a case of confirmation bias, meaning that the researcher stopped recruitment when the hypothesis was verified. It could also mean that some of these results are less accurate, due to lower number of participants, since there is uncertainty towards the validity of the results derived from RCTs with less than 100 participants.

How implementation factors affect the outcomes and heterogeneity

Heterogeneity has been found in the included studies regarding the study location, the included long-term conditions and the medication adherence measurement method. Although, the included study types were also heterogenic (Table 2), this does not seem to affect the general trend that the use of PHR has a positive impact in medication adherence. Heterogeneity has also been identified in participants' demographics and confounding factors (Table 2).

Although expected otherwise, the duration of the follow-up in RCT studies does not seem to affect the outcomes, since the majority of the included RCTs produced positive results. There is however and indication that three out of four RCT studies that did not produce positive results had a 12 months follow-up. This observation is in-line with the general idea of the field being new and there are no global standards that dictate the design of PHRs. Another interesting fact is that the studies that were either observational or literature reviews produced statistically more positive results than the RCTs.

Quality assessment

The inter-rater reliability between EA and PS was calculated to k=0.88, which indicates that the reliability of the quality assessment is likely to be high. Overall, 35 studies matched our inclusion criteria. 12 of these studies were excluded due to low quality of evidence, 10 were graded as high quality of evidence and the remaining 13 as moderate quality of evidence. The detailed quality assessment table based on the GRADE approach can be found in the additional file.

Error! Reference source not found. illustrates the overall risk of bias for this study. The details behind this diagram are provided as additional file.

DISCUSSION

In this section we reflect upon the principal themes and overall conclusions from the literature review. A first impression after the initial data analysis was that too few studies actually mentioned the term PHR. In the majority of the cases we had to critique the intervention of the inclusion criteria based on our PHR definition. This systematic review included 23 studies of multiple study types and identified 12 different PHR design features. Although 12 different PHR design features were identified, there are no specific guidelines that can be derived from the results. Overall, 74% (n=17) of the included studies found that the use of a PHR has increased medication adherence. Based on the number of studies that identified positive results, the fact that 8 out of the 10 high quality studies identified positive results and that no study indicated a negative effect on medication

adherence, we conclude that there is a reasonable indication that PHRs can have an overall positive effect on medication adherence. However, due to the high heterogeneity in medication adherence measurements, reporting styles and study types, we were unable to group and quantify the results in study level. It is of course possible that the absence of negative results is due to publication bias.

Reminders and medication management are the most commonly used PHR design feature, since only four of the included 23 studies do not include either of the two. The generated clusters paint a similar picture. The cluster that produces the best results is medication management and patient's blog (100% of studies in this cluster produce positive results), followed by personalisation & tailoring (92% of studies in this cluster produce positive results) and reminder and medical appointment management (80% of studies in this cluster produce positive results). These findings are also consistent with the existing literature, which identifies reminders as a generally helpful tool for patients to remember to take or order their medication.[45]

Two groups of patients have been identified in this literature review for further analysis, to find which of the PHR design features work best for them. The most positive results for diabetic participants were identified by four studies [23,38–40] that used PHRs. Furthermore, for participants with HIV, three studies were identified producing positive results [35–37] that used at least personalisation and tailoring design feature and reminders. Mixed associations were found between patients demographics, their PHR usage and medication adherence. Taking into account the median age confounding factor of the participants, then it is apparent that the younger the participants, the more positive results identified. This is also supported in the general academic literature that suggest that technological literacy levels are higher in younger adult population.[46,47]

Furthermore, the less participants a study included the more positive the results appeared to be. This in fact may cause problems in the quality of evidence for the included studies and this literature review; hence our suggestion to interpret the results with caution. There is a proven link between the sample size of an RCT and the statistical significance of its result.[48] According to Faber *et al*,[49] the small sample size might increase the chance of a false-positive and the study might not reach to a evident conclusion.

The 'other' bias category has the highest risk of bias of all the assessed risks, which is in line with the key findings of this and other related studies,[50] resulting in a probable overestimation of PHR effect on medication adherence and potentially echoing a form of recall bias.[51] Although some degree of bias is considered unavoidable, the high risk of bias identified in the included studies and the generally moderate quality of evidence presented in them also reflects the uncertainty on this field and the need for further research on both PHRs and medication adherence. A PHR design feature that is not mentioned in the included literature is security. This might be happening due to the inclusion/exclusion criteria of this systematic review, since the security of the data does not seem to affect patients' medication adherence. Another limitation is that we included English papers published in the last 15 years, due to time and cost constraints. Furthermore, the small number of participants in the studies is commonly known to overestimate the effect of an intervention, fact which is noticeable in the included studies.

FUNDING STATEMENT

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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COMPETING INTERESTS STATEMENT

None declared.

DATA SHARING STATEMENT

No additional data are available.

PATIENT AND PUBLIC INVOLVEMENT

PPI has already been involved in the design of this research. On 22 of June 2018, a PPI focus group with 8 participants took place at the University of Portsmouth. This group's suggestions are taken into consideration by the research team. The PPI group approved the focus of this review and provided guidelines for future research.

PATIENT CONSENT

Not required.

AUTHOR CONTRIBUTION

EA drafted the manuscript, and is the guarantor of the review. PJS revised the manuscript multiple times for methodological and intellectual content. HH revised the manuscript twice for methodological, conceptual and intellectual content from a pharmaceuticals' perspective. AG also revised the manuscript for methodological, conceptual and intellectual content and also contributed in the abstract design. The final version of the manuscript was approved by all three authors.

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Literature review

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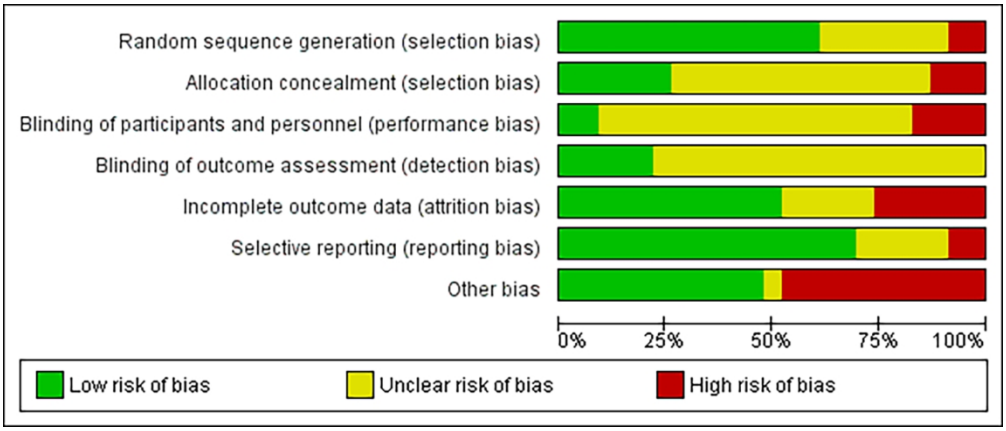
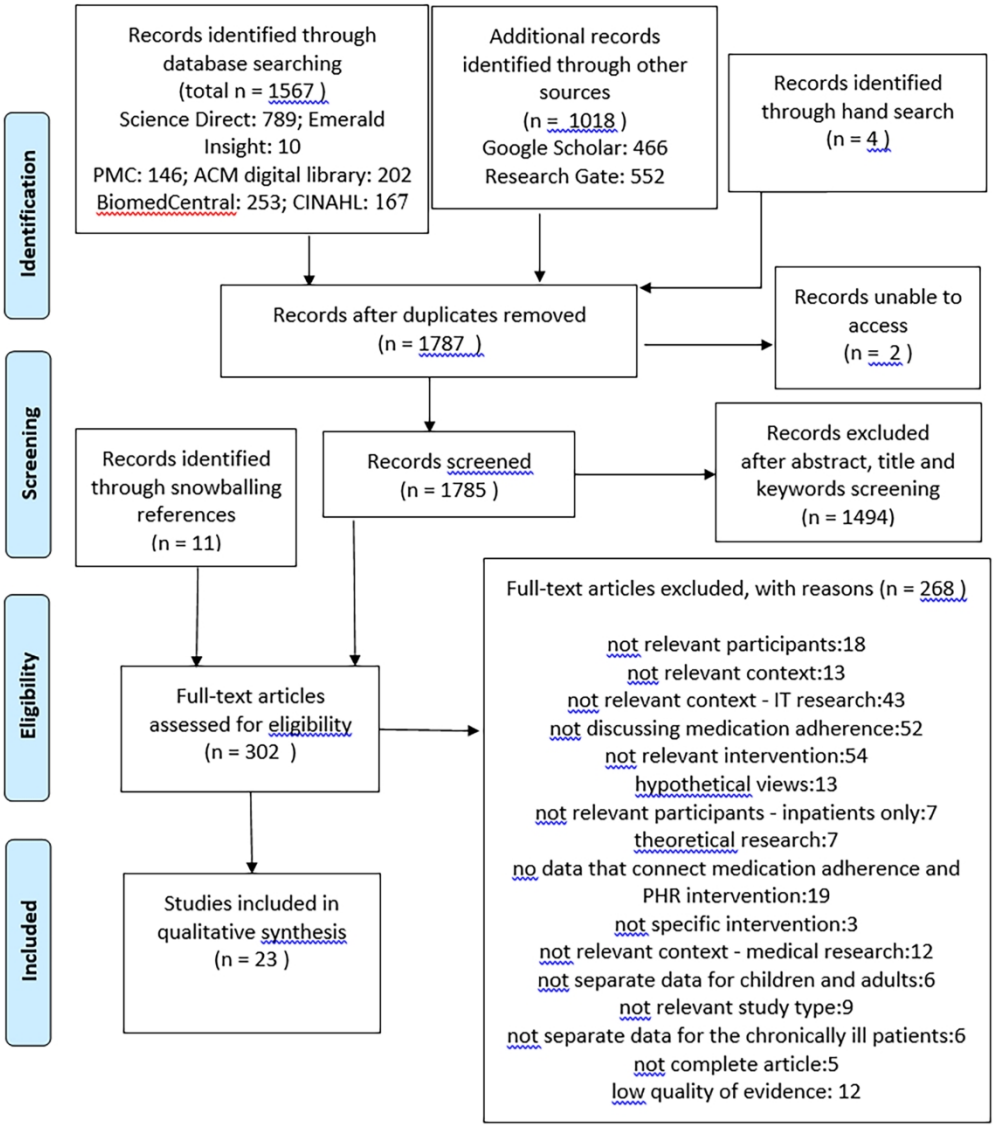


Risk of bias graph

160x67mm (300 x 300 DPI)



Overview of the literature selection process

204x230mm (300 x 300 DPI)

Study	Study Type	Starting Point	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Quality of evidence
Allam 2015	RCT	high	Unclear (-1)	Unclear (-1)	Unlikely	Unclear (-1)	Unlikely	Low
Chrischilles 2014	RCT	high	Unclear (-1)	Unlikely	Unclear (-1)	High (-2)	Unlikely	Low
Dalgaard 2013	Case series	low	High (-2)	Unlikely	Unlikely	High (-2)	Unlikely	Very Low
Fabravanti 2015	RCT	high	Unclear (-1)	Unlikely	Unlikely	Unclear (-1)	Unclear (-1)	Moderate
Foreman 2012	cohort study	moderate	Unclear (-1)	Unlikely	Unlikely	Unclear (-1)	Unlikely	Low
Glaser 2017	RCT	high	No risk of bias	Unlikely	Unlikely	Unlikely	Unlikely	High
Glasgow 2012	RCT	high	Unclear (-1)	Unclear (-1)	Unlikely	Unclear (-1)	Unlikely	Low
Hou 2012	cohort study	moderate	Unclear (-1)	High (-2)	Unlikely	Unlikely	Unlikely	Low
Kaplan 2013	systematic literature review	high	Unclear (-1)	Unclear (-1)	Unlikely	Unclear (-1)	High (-2)	Low
Keith 2013	cross sectional study	low	Unclear (-1)	Unlikely	Unlikely	Unlikely	Unlikely	Low
Lee 2014	RCT	high	High (-2)	High (-2)	Unlikely	Unlikely	Unlikely	Low
Luque 2012	RCT	high	Unclear (-1)	Unlikely	Unlikely	Unlikely	Unclear (-1)	Moderate
McDermott 2013	systematic literature review	high	Unclear (-1)	Unlikely	Unclear (-1)	Unlikely	Unlikely	Moderate
McGillicuddy 2013	RCT	high	Unclear (-1)	Unlikely	Unclear (-1)	Unclear (-1)	Unclear (-1)	Low
McLean 2016	systematic literature review with m	high	Unclear (-1)	Unlikely	Unlikely	Unlikely	Unlikely	High
Mistry 2015	systematic literature review	high	Unclear (-1)	Unlikely	Unlikely	Unlikely	Unlikely	High
Morton 2017	systematic literature review	high	Unclear (-1)	Unlikely	Unlikely	Unclear (-1)	Unlikely	Moderate
Naslund 2017	narrative literature review	high	High (-2)	Unlikely	Unlikely	Unclear (-1)	Unclear (-1)	Low
Park 2014	systematic literature review	high	Unclear (-1)	Unlikely	Unlikely	Unlikely	Unclear	High
Patel 2013	RCT	high	Unclear (-1)	Unlikely	Unlikely	High (-2)	Unclear (-1)	Low
Riva 2014	RCT	high	Unclear (-1)	Unlikely	Unlikely	Unclear (-1)	Unlikely	Moderate
Siu 2017	quasi-experimental	moderate	Unclear (-1)	Unlikely	Unlikely	Unclear (-1)	Unlikely	Low
Stephani 2016	systematic literature review	high	Unclear (-1)	Unlikely	Unlikely	Unclear (-1)	Unclear	Moderate
Tang 2013	RCT	high	High (-2)	Unlikely	Unlikely	Unlikely	Unlikely	Moderate
Westergaard 2017	Qualitative study	moderate	Unclear (-1)	Unlikely	Unclear (-1)	Unlikely	Unlikely	Low
Yu 2014	cohort study	moderate	Unclear (-1)	High (-2)	Unlikely	Unlikely	Unlikely	Low
Zettl 2016	cohort study	moderate	Unclear (-1)	Unlikely	Unlikely	Unclear (-1)	Unlikely	Low


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Allam 2015
Chrischilles 2014
Dabbs 2016
Dorr 2007
Fioravanti 2015
Glaser 2017
Glasgow 2012
Grant 2008
Harrison 2014
Lakshminarayana 2017
Luque 2012
McDermott 2013
McLean 2016
Mira 2014
Mistry 2015
Morton 2017
Park 2014
Perera 2014
Riva 2014
Stephani 2016
Tang 2013
Westergaard 2017
Zettl 2016

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
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3-4
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.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
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.	4
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).	4
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.	13

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).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
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
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.	7-10
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
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.	7-10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13
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).	14
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).	14-15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
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.	15

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

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

BMJ Open

What are the important design features of personal health records to improve medication adherence for patients with long term conditions? A systematic literature review.

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Primary Subject Heading:	Health informatics
Secondary Subject Heading:	Public health
Keywords:	personal health record, medication adherence, medical informatics, systematic literature review, long-term conditions, PHR

What are the important design features of personal health records to improve medication adherence for patients with long term conditions? A systematic literature review.

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Literature review

Word Count: 3495

KEYWORDS

Personal health record, medication adherence, medical informatics, systematic literature review, long-term conditions

ABSTRACT

Objectives: This systematic literature review aims to identify important design features of the electronic personal health record (PHR) that may improve medication adherence in the adult population with long-term conditions.

Data sources: PubMed (including MEDLINE), CINAHL, Science Direct (including EMBASE), BioMed Central, ACM digital, Emerald Insight, Google Scholar and Research Gate.

Methods: Studies published between 1/1/2002 to 31/5/2018, in English were included if the participants were adults, with at least one long-term condition, able to self-administer their medication and were treated in primary care settings. The quality of evidence was assessed with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system and the risk of bias was appraised using the Cochrane risk of bias tool.

Results: From a total of 27 studies that matched the inclusion criteria, 12 were excluded due to low quality of evidence, 10 were rated moderate and 5 were high quality. All the included studies had low sample size and limited follow-up duration. 13 of the included studies found that the use of a PHR has increased medication adherence. The identified design features are reminders, education, personalisation and tailoring, feedback and alerts, gamification, medication management, medical appointment management, diary and self-monitoring, health condition management, set goals, patient's blog and tethered. It was impossible to draw conclusions as to which feature is important to what group of patients and why. The most frequently identified conditions were HIV and diabetes. This review did not identify any papers with negative results. It was not possible to numerically aggregate the PHR effect due to high heterogeneity of the medication adherence measurement, study type, participants and PHRs used.

Conclusion: Although we found recurrent evidence that PHRs can improve medication adherence, there is little evidence to date to indicate which design features facilitate this process.

Registration: PROSPERO CRD42017060542

Literature review

ARTICLE SUMMARY

Strengths and limitations of this study

- This is a systematic literature review that follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines;
- The protocol was published before conducting the study to avoid data-driven decisions;
- A comprehensive literature search was carried out using eight major research paper databases, hand-searching and snowballing;
- All included studies were quality assessed using well-cited tools and documentation;
- A study limitation is that only studies published in English language were included

INTRODUCTION

A 2018 healthcare consultant report calls for focusing on healthcare value instead of increasing the size of the current systems to accommodate for the rising demand.[1] Healthcare expenditures were 16.5% of GDP in USA and 11.5% of GDP for Switzerland in 2016.[1] NHS policy anticipates that increasing usage of health apps by patients will reduce demand on healthcare services.[2] *The NHS Long Term Plan*[3] policy document focuses on increasing personalisation in healthcare to improve quality of life and public health and aspires that information and communication technology (ICT) can reduce healthcare costs and improve healthcare outcomes over the next five years. This assertion, however, is not based upon scientific research, so the claimed benefits remain aspirational.

Currently, 74% of UK nationals older than 45 years old and almost all younger than 45 years old adults are using the internet nearly every day.[4] Based on the results of a 2017 US survey, roughly 40% of people living with a long-term condition were interested in using technology to assist them with medication, diagnosis, test results and managing their condition in their home environment.[5]

A form of ICT that could potentially benefit the patients and the healthcare services is the electronic personal health record (PHR). A PHR has been defined as: “online systems that include collections of patients’ healthcare and medical data, which utilise health informatics standards to enable patients to share, organize and manage these data according to their own views”.[6] Some of the claimed benefits of PHRs are the ability of PHR to improve patient outcomes, decrease care cost, allow patients the ability to self-manage their health, increase access to care especially in remote areas, empower patients and improve medication adherence.[7,8]

Medication adherence is a well-known challenge in healthcare,[9,10] and is related to a large number of factors such as side effects,[11] forgetfulness,[9] or effective self-management[12] and is affected by psychological factors and beliefs.[12] Medication adherence can be defined as “the extent to which a person’s behaviour towards their medication intake, corresponds with agreed recommendations from a health care provider”.[10] The World Health Organization (WHO) reported that in developed countries the medication adherence in patients with long-term conditions averages to fifty percent.[13] There is limited evidence whether PHRs actually improve medication adherence in chronically ill adults and no evidence synthesis as to which PHR design features are the most effective.

Polypharmacy refers to the simultaneous use of multiple medications and has associated with several poor health outcomes including medication adherence.[14–16] The effects of poor medication adherence are greater for people with polypharmacy,[16]This effect is greater since the

number of people with also with multiple long-term conditions is rising.[17] It is estimated that in UK, more than a third of patients with at least one long term illness do not adhere to their medication regime.[18]

A number of systems are currently in practice to use information and communication technologies (ICT) in order to store, manage and employ health and medical information. These ICTs are developed by coders who are implementing Human-Computer Interaction (HCI) principles.[19] The HCI discipline is used to improve the usability of the software to developers, especially in healthcare settings.[20] The NHS standards for PHRs[21] provide guidance on good practice for their development in England, but they do not provide enough details or guidelines on what design features should a PHR include nor evidence on how these features impact health outcomes.

Although a number of strategies and interventions have been identified to assist patients' medication adherence,[22,23] the number of approaches related to PHRs is surprisingly low. This is surprising since the limited success that traditional approaches to support adherence have had and that technical interventions may easily be combined with other categories of interventions such as behavioural to address and potentially improve medication adherence.[24]

This is the first systematic literature review that aims to identify important design features of the PHR that may improve medication adherence in the adult population with long-term conditions.

Objectives

Primary objective

Identify the important design features of the PHR that may have improved medication adherence in the adult population with long-term conditions.

Secondary objectives

- Identify the PHR design features that may have improved medication adherence in the cases of:
    - polypharmacy;
    - specific long term condition groups;
- Identify if there was a correlation between participants' demographic characteristics, their usage of PHRs and their medication adherence;
- Explore how implementation factors affected medication adherence.

METHODS

This systematic review is registered in the prospective register of systematic reviews (PROSPERO), registration number CRD42017060542 and follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[25] The PRISMA checklist is provided as an additional file. The protocol for this study is published.[6]

Study eligibility and selection

This review's inclusion and exclusion criteria are illustrated in Table 1 and are detailed in the published protocol.[6] As a result of the peer review process, we have decided to make a change to our published protocol and to exclude systematic literature reviews and include only primary studies.

There have been no deviations from the protocol.

Literature review

Table 1 Summary of the PICOS elements included and excluded in the systematic review

	Inclusion criteria	Exclusion criteria
Participants		
	Humans Adults with at least one long term condition Patients that can self-administer their medication Patients that are able to communicate freely and able to self-manage their medication. Patients treated outside the hospital only	Animals Pregnant, cancer or terminally ill patients Adults with medically serious problems that are not classified as long term conditions Patients that require assistance with taking their medication Patients unable to communicate or unable to self-manage their medication. Inpatients or patients living in care homes
Intervention		
	Interventions of any type, intensity and frequency, that aim to investigate the effect of electronic PHRs in medication adherence, concordance, compliance or persistence.	N/A
Comparators		
	Non-PHR	No comparison has been made with no-PHR or with usual care
Outcome		
	Any outcome related to the effect of electronic PHRs in medication adherence, concordance, compliance or persistence.	N/A
Study design/type		
	Primary studies published in the last fifteen years, without any geographical restriction.	Abstract-only reports without any references, commercial studies, party political statements, general discussion papers, magazine or newspaper articles, withdrawn abstracts or articles, protocols of reviews or literature reviews
Quality of the Studies		
	Studies with Moderate or High quality	Studies with Low and very low quality.

Literature search

Mendeley software[26] was used as the bibliographic software. One author (EA) scanned the titles and abstracts and excluded studies that clearly did not meet the inclusion criteria. Full-text versions of the remaining articles were obtained and screened by the same author, using the criteria listed on Table 1. All the excluded studies were listed with at least one reason for exclusion. In case of uncertainty, the author PS was advised and there was a discussion until an agreement was made.

Literature review

The reference lists of the included studies were examined to identify additional relevant literature. A hand-search of JMIR Medical Informatics, BMC Medical Informatics and Decision Making and BMJ Open was conducted by EA to identify further literature, as they were the three most cited and most impactful journals in the search we had done.

The full search strategy can be found in supplementary file. The search dates are January 1st, 2002 to May 31st, 2018 and the search terms are:

> (phr OR “personal health record” OR "patient portal") AND adult* AND (“chronic disease” OR “chronic illness” OR “chronic condition” OR “long term disease” OR “long term illness” OR “long term condition”) AND ("medication compliance" OR "medication adherence" OR "medication concordance" OR "medication persistence")

Data extraction and analysis

EA reviewed and extracted the all literature and the data in the predefined data extraction forms.[6] The data extraction forms were designed by PS and EA to collect all the necessary data, based on the National Institute for Health and Care Excellence (NICE) data extraction forms[27] and the research questions. The completed data extraction forms, the initial and complete narrative analysis of the generated data was performed by EA and face validated by PS,[6] who did not review the excluded literature.

Quality assessment

The quality of all included studies was assessed by the first author (EA) and 25% of the included studies were assessed by the second author (PS). Cohen’s Kappa (k) inter-rater reliability measure[28] was calculated. The Joanna Briggs Institute (JBI) critical appraisal questionnaires were used to implement the GRADE approach[29] of quality assessment of the included studies. The GRADE approach is proposed by the Cochrane Collaboration[30] and it favours the JBI critical appraisal tools.[31]

The final quality scores per paper (Table 2) were assigned based upon five factors: risk of bias,[32] inconsistency,[33] indirectness,[34] imprecision[35] and publication bias.[36] All the studies were graded based on their study type, for example RCTs and systematic literature reviews started as high quality studies. Using the GRADE categories we started from the highest possible score based on the study’s study type, using the JBI questions to extract data per paper for the GRADE scoring, reducing the quality for each instance of the factors mentioned above.

Patient and public involvement

PPI has already been involved in the design of this research. On 22 of June 2018, a PPI focus group with 8 participants took place at the University of Portsmouth. This group's suggestions are taken into consideration by the research team. The PPI group approved the focus of this review and provided guidelines for future research.

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RESULTS

Literature search results

Figure 1 illustrates the literature search and selection method, presenting explanations for the exclusion of studies. Once duplicates were removed, a total of 1787 original works were identified and 15 were finally included in the qualitative synthesis.

Characteristics of included studies

This review includes studies conducted in the USA (n=7), in Switzerland (n=2), in Canada (n=1), UK (n=1), Germany (n=1), Italy &Czech Republic (n=1), New Zealand (n=1) and Spain (n=1). Most studies had included participants, which have at least one long term condition (n=9), diabetes (n= 4) and HIV (n=3). Studies were published in 2017 (n=4), 2014 (n=4), 2016 (n=3), 2015 (n=2), 2013 (n=1) and 2008 (n=1). The majority of the included studies (n = 13) reported a positive result in terms of the impact on medication adherence, with two studies found no difference.[37,38] No study identified negative results. Five out of five high quality studies and eight out of 10 moderate quality studies found positive results with medication adherence. The main study characteristics are illustrated in Table 2.

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Table 2 Included Primary Studies Characteristics

Study	Study type	Participants				Intervention	Control		Medication adherence assessment	Long Term Condition	Follow-up (months)	Medication adherence results	Quality
		Number	Mean Age	Male %	Education (>= high school %)	Name	Number	Type of Care					
Allam (2015)	RCT	155	57.96	54.1	76.1	ONESelf	40	Usual care	Prescription Opioid Misuse Index	Rheumatoid arthritis	4	Positive	Moderate
Chrischilles (2014)	RCT	1075	72.3	43.2	98.7	Iowa PHR	273	Usual care	Self-reported	At least one	12	No difference	Moderate
Dabbs (2016)	RCT	201	62	55.2	94	Pocket PATH	Not stated	Usual care	Health Habits Survey	Lung transplant recipients (LTRs)	12	Positive	High
Fioravanti (2015)	RCT	51	Not stated	Not stated	Not stated	METABO system	25	Usual care	Self-reported	Diabetes (all types)	1	Positive	Moderate
Glaser (2017)	RCT	221	Not stated	58.4	72	PACE	Not stated	Usual care	Lab results	At least one	9	Positive	High
Glasgow (2012)	RCT	332	61.4	95	86	My Path to Health Life	Not stated	Enhanced Usual care	Hill-Bone scale	Diabetes type 2	12	No difference	Moderate
Grant (2008)	RCT	244	Not stated	51	Not stated	DM PHR	118	Usual care	Medication initiation or dosage adjustment	Diabetes type 2	12	Positive	High
Lakshminarayana (2017)	RCT	201	60.3	60.7		Parkinson's Tracker	90	Usual care	MMAS-8	Parkinson's disease (PD)	4	Positive	Moderate

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Luque (2012)	RCT	29	48	55	69	MyMedical	n/a	Usual care	Self-reported	HIV	2	Positive	Moderate
Mira (2014)	RCT	99	71.9	55.5	Not stated	ALICE	48	Usual care	MMAS-4	At least one	11	Positive	Moderate
Perera (2014)	RCT	28	46	93	Not stated	Not named	11	Usual care	MARS, pharmacy dispensing records, and lab tests	HIV	3	Positive	Moderate
Riva (2014)	RCT	51	47.5	49	76.4	ONESelf	24	Usual care	Prescription Medication Use and Perception of Risk Instrument	Chronic back pain (CBP)	5	Positive	High
Tang (2013)	RCT	415	53.7	60	94.3	PHCP	213	Usual care	diabetes control	Diabetes type 2	12	Positive	High
Westergaard (2017)	Qualitative	19	49.3	63	74	mPeer2Peer	Not stated	Usual care	Self-reported	HIV	n/a	Positive	Moderate
Zettl (2016)	Cohort Study	669	38.4	29	28	BETAPATH	330	Paper based PDA	Number of injections per study interval.	Multiple sclerosis (MS)	24	Positive	Moderate

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Primary objective

Table 3 presents the PHR design features that were identified in the literature and are the generated themes of this literature review. The definitions of the PHR design features derive from commercial PHRs that are implementing them or the wider literature regarding PHRs and personal experience, since there are no International Standards Organization (ISO) standards or universally accepted terminology.

Table 3 PHR design features

Feature	Definition	Medication adherence results by study	
		Positive	No difference
Reminder	Reminders to take medication or to reorder their prescriptions, agnostic to the patient's chronic condition, demographics or any other external factor.	11	1
Education	Includes smaller features, like search bars and views, which can improve the user's health literacy and understanding of their condition.	3	2
Personalisation and tailoring	The personalisation involves presenting a health message specific to the individual patient's condition and demographic characteristics, whilst tailoring involves developing a PHR based on the individual's characteristics.[39]	8	1
Feedback and alerts	Medical emergency alerts in the form of a press button alert or SMS, such as the ones a user may find in the MyALERT PHR.[40]	10	2
Gamification	An umbrella term that includes the use of game design characteristics in non-game contexts.[41]	4	1
Medication management	Includes all the features that a chronically ill patient may need to conform to everyday life.[42]	10	2
Medical appointment management	Medically related appointment tracking, re-scheduling and arrangement.[43]	2	-
Diary and self-monitoring	A combination of features related to health or medication intake monitoring.[44]	8	2
Health condition management	Includes all the lab and medical tests results and integration of existing clinical data.[39]	3	1
Set goals	Includes all the elements that are necessary for setting and managing goals.	2	1
Patient's blog	Includes sharing in social media or blogging regarding health.[45]	1	-
Tethered	Are the PHRs which are connected with an electronic health record (EHR).[46]	2	-

All the PHR design features, which are constitute the themes derived from our thematic analysis,[47] are interlinked and overlap. NVivo 11 was used to cluster our codes into potentially more comprehensive themes. The initial themes were clustered together based on coding similarity, which means that if there were coding many of the same included studies, they then were clustered together.

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- reminder and medical appointment management (used in 2 studies)
- tethered (used in 2 studies)
- diary and self-monitoring (used in 10 studies)
- feedback and alerts and health condition management (used in 4 studies)
- medication management and patients blog (used in 1 studies)
- personalisation & tailoring, gamification, education, set goals (used in 10 studies)

Secondary objectives

PHR design features that improve medication adherence in case of polypharmacy

Even though multiple papers are including polypharmacy or multi-morbidity factors about their participants, they do not explore whether there is a correlation or an association between polypharmacy and the PHR usage or medication adherence improvement or not. There is a trend that the more medications a person uses the less a reminder helps, but this is not a conclusion directly supported by the data, but an argument emerging from multiple studies.[38,45,48,49]

PHR design features that improve medication adherence for specific long term condition groups

This research identified a number of chronic conditions. However, only diabetes and HIV can be used to analyse the impact that the PHR design features are having in medication adherence, since the rest of the conditions are included in just one study.

HIV

Three studies have been included that discuss how the use of PHRs affect medication adherence of adults with HIV.[49–51] All three studies produced positive results, having a very small (less than 50) number of participants that are also predominantly male and younger than 50 years old. Two studies are RCTs,[50,51] having follow-up duration of 2 to 3 months and the other one is a qualitative study[49] without any follow-up. All three studies include the personalisation and tailoring design feature, two of the studies use reminders, one study uses feedback and alerts and health condition management and one other study uses diary and self-monitoring design feature.

Diabetes

Four studies have been included that discuss how the use of PHRs affect medication adherence of adults with diabetes.[37,52–54] All studies found positive results regarding medication adherence, apart from Glasgow *et al.*[37] Three studies used diary and self-monitoring[37,52,53] or personalisation and tailoring,[37,52–54] three studies used education and set goals[37,52,53] or gamification[37,52,54] and one[53] used feedback and alerts and health condition management PHR design features. The studies' follow-up duration was 12 months apart from Fioravanti *et al*,[52] which was 1 month.

Association between participants' demographic characteristics, their usage of PHRs and their medication adherence

Data regarding patients' demographics and medication adherence were collected and analysed. Only two[50,55] of the 15 studies provide a detailed description of the participants' ethnicity. Two studies[55,56] are also providing data regarding the technology literacy of the participants and two other studies[37,50] provide data for the health literacy of the participants.

Twelve of the 15 studies provided age group details, which illustrate that the younger the participants, the more positive results regarding medication adherence were identified. This could

be due to the presumed technological literacy of younger generations, however it was impossible to account for this confounding factor, since no data were supplied. Also the lower the number of participants in an experimental study (less than 251), the higher the impact of PHR in medication adherence. This could arguably illustrate a case of confirmation bias, meaning that the researcher stopped recruitment when the hypothesis was verified. It could also mean that some of these results are less accurate, due to lower number of participants, since there is uncertainty towards the validity of the results derived from RCTs with less than 100 participants.[57]

How implementation factors affect the outcomes and heterogeneity

Heterogeneity has been found in the included studies regarding the study location, the included long-term conditions and the medication adherence measurement method. Although, the included study types were also heterogenic (Table 2), this does not seem to affect the general trend that the use of PHR has a positive impact in medication adherence. Heterogeneity has also been identified in participants' demographics and confounding factors (Table 2).

Although expected otherwise, the duration of the follow-up in RCT studies does not seem to affect the outcomes, since the majority of the included RCTs produced positive results. There is however and indication that three out of four RCT studies that did not produce positive results had a 12 months follow-up. This observation is in-line with the general idea of the field being new and there are no global standards that dictate the design of PHRs. Another interesting fact is that the studies that were either observational or literature reviews produced statistically more positive results than the RCTs.

Quality assessment

The inter-rater reliability for quality assessment was calculated to k=0.88, which indicates high reliability of the quality assessment. Overall, 27 studies matched our inclusion criteria. 12 of these studies were excluded due to low quality of evidence, five were graded as high quality of evidence and the remaining 10 as moderate quality of evidence. The detailed quality assessment table based on the GRADE approach can be found in the additional file.

Figure 2 illustrates the overall risk of bias for this study. The details behind this diagram and the overall quality assessment are provided as additional file.

DISCUSSION

In this section we reflect upon the principal themes and overall conclusions from the literature review. A first impression after the initial data analysis was that too few studies actually mentioned the term PHR. In the majority of the cases we had to critique the intervention of the inclusion criteria based on our PHR definition. This systematic review included 15 primary studies of multiple study types and identified 12 different PHR design features. Although 12 different PHR design features were identified, there are no specific guidelines that can be derived from the results. Overall, 87% (n=13) of the included studies found that the use of a PHR has increased medication adherence. Based on the number of studies that identified positive results, the fact that 8 out of the 10 high quality studies identified positive results and that no study indicated a negative effect on medication adherence, we conclude that there is a reasonable indication that PHRs can have an overall positive effect on medication adherence. However, due to the high heterogeneity in medication adherence measurements, reporting styles and study types, we were unable to group

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and quantify the results in study level. It is of course possible that the absence of negative results is due to publication bias.

Reminders, feedback and alerts and medication management are the most commonly used PHR design feature, since all studies include at least one of the three. These findings are also consistent with the existing literature, which identifies reminders, and medication management as the most commonly used features that assist patients with their medication intake.[58–62] The design features with the most positive effect for patients' medication adherence were patient's blog, tethered and medical appointment management. This could arguably be since these features are also the least used, since the medication appointment management has the most positive results in the relevant literature.[59–65] The generated clusters paint a similar picture. The cluster that produces the best results is personalisation & tailoring, gamification, education and set goals (92% of studies in this cluster produce positive results) and reminder and medical appointment management (80% of studies in this cluster produce positive results).

Two groups of patients have been identified in this literature review for further analysis, to find which of the PHR design features work best for them. The most positive results for diabetic participants were identified by three studies[52–54] that used PHRs. Furthermore, for participants with HIV, three studies were identified producing positive results[49–51] that used at least personalisation and tailoring design feature and reminders. Mixed associations were found between patients demographics, their PHR usage and medication adherence. Taking into account the median age confounding factor of the participants, then it is apparent that the younger the participants, the more positive results identified. This is also supported in the general academic literature that suggest that technological literacy levels are higher in younger adult population.[66,67]

Furthermore, the less participants a study included the more positive the results appeared to be. This in fact may cause problems in the quality of evidence for the included studies and this literature review; hence our suggestion to interpret the results with caution. There is a proven link between the sample size of an RCT and the statistical significance of its result.[68] According to Faber *et al*,[69] the small sample size might increase the chance of a false-positive and the study might not reach to a evident conclusion.

The 'other' bias category has the highest risk of bias of all the assessed risks, which is in line with the key findings of this and other related studies,[70] resulting in a probable overestimation of PHR effect on medication adherence and potentially echoing a form of recall bias.[71] Although some degree of bias is considered unavoidable, the high risk of bias identified in the included studies and the generally moderate quality of evidence presented in them also reflects the uncertainty on this field and the need for further research on both PHRs and medication adherence. A PHR design feature that is not mentioned in the included literature is security. This might be happening due to the inclusion/exclusion criteria of this systematic review, since the security of the data does not seem to affect patients' medication adherence. Another limitation is that we included English papers published in the last 15 years, due to time and cost constraints. Screening of the studies and data collection was conducted by EA and only face validated by PS, therefore this is also a significant limitation. Furthermore, the small number of participants in the studies is commonly known to overestimate the effect of an intervention, fact which is noticeable in the included studies.

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COMPETING INTERESTS STATEMENT

None declared.

DATA SHARING STATEMENT

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

PATIENT CONSENT

Not required.

AUTHOR CONTRIBUTION

EA drafted the manuscript, and is the guarantor of the review. PJS revised the manuscript multiple times for methodological and intellectual content. HH revised the manuscript twice for methodological, conceptual and intellectual content from a pharmaceuticals' perspective. AG also revised the manuscript for methodological, conceptual and intellectual content and also contributed in the abstract design. The final version of the manuscript was approved by all three authors.

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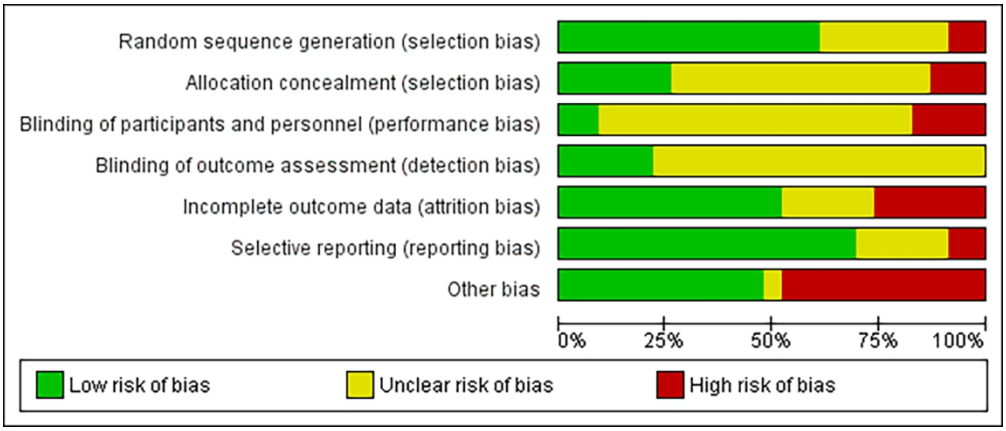
FIGURE LEGENDS

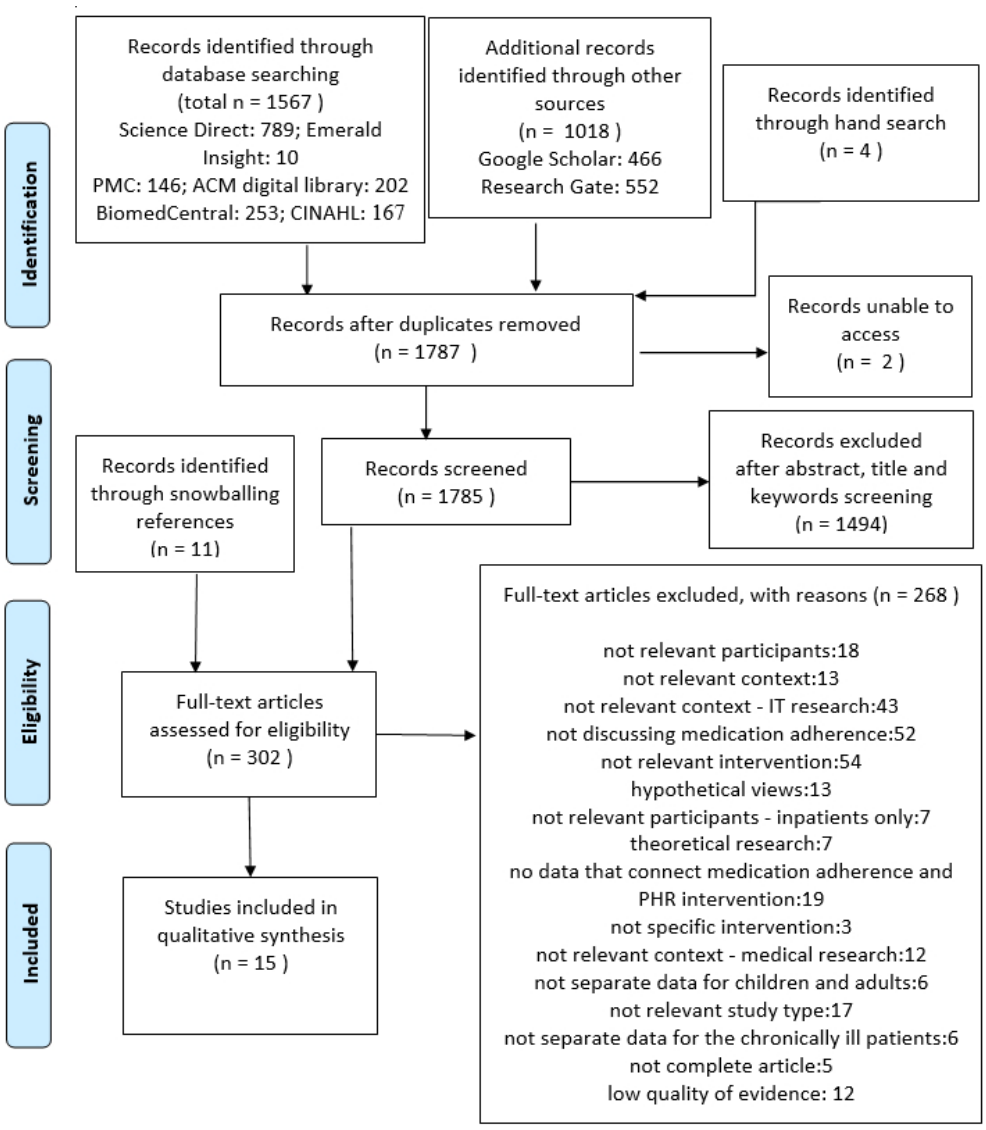
Figure 1 PRISMA literature search and selection method diagram

Figure 2 Overall risk of bias



Risk of bias graph

160x67mm (300 x 300 DPI)



PRISMA literature search and selection method diagram

Study	Study Type	Starting Point	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Quality of evidence
Allam 2015	RCT	high	Unclear (-1)	Unclear (-1)	Unlikely	Unclear (-1)	Unlikely	Low
Chrischilles 2014	RCT	high	Unclear (-1)	Unlikely	Unclear (-1)	High (-2)	Unlikely	Low
Dalgaard 2013	Case series	low	High (-2)	Unlikely	Unlikely	High (-2)	Unlikely	Very Low
Fabravanti 2015	RCT	high	Unclear (-1)	Unlikely	Unlikely	Unclear (-1)	Unclear (-1)	Moderate
Foreman 2012	cohort study	moderate	Unclear (-1)	Unlikely	Unlikely	Unclear (-1)	Unlikely	Low
Glaser 2017	RCT	high	No risk of bias	Unlikely	Unlikely	Unlikely	Unlikely	High
Glasgow 2012	RCT	high	Unclear (-1)	Unclear (-1)	Unlikely	Unclear (-1)	Unlikely	Low
Hou 2012	cohort study	moderate	Unclear (-1)	High (-2)	Unlikely	Unlikely	Unlikely	Low
Kaplan 2013	systematic literature review	high	Unclear (-1)	Unclear (-1)	Unlikely	Unclear (-1)	High (-2)	Low
Keith 2013	cross sectional study	low	Unclear (-1)	Unlikely	Unlikely	Unlikely	Unlikely	Low
Lee 2014	RCT	high	High (-2)	High (-2)	Unlikely	Unlikely	Unlikely	Low
Luque 2012	RCT	high	Unclear (-1)	Unlikely	Unlikely	Unlikely	Unclear (-1)	Moderate
McDermott 2013	systematic literature review	high	Unclear (-1)	Unlikely	Unclear (-1)	Unlikely	Unlikely	Moderate
McGillicuddy 2013	RCT	high	Unclear (-1)	Unlikely	Unclear (-1)	Unclear (-1)	Unclear (-1)	Low
McLean 2016	systematic literature review with m	high	Unclear (-1)	Unlikely	Unlikely	Unlikely	Unlikely	High
Mistry 2015	systematic literature review	high	Unclear (-1)	Unlikely	Unlikely	Unlikely	Unlikely	High
Morton 2017	systematic literature review	high	Unclear (-1)	Unlikely	Unlikely	Unclear (-1)	Unlikely	Moderate
Naslund 2017	narrative literature review	high	High (-2)	Unlikely	Unlikely	Unclear (-1)	Unclear (-1)	Low
Park 2014	systematic literature review	high	Unclear (-1)	Unlikely	Unlikely	Unlikely	Unclear	High
Patel 2013	RCT	high	Unclear (-1)	Unlikely	Unlikely	High (-2)	Unclear (-1)	Low
Riva 2014	RCT	high	Unclear (-1)	Unlikely	Unlikely	Unclear (-1)	Unlikely	Moderate
Siu 2017	quasi-experimental	moderate	Unclear (-1)	Unlikely	Unlikely	Unclear (-1)	Unlikely	Low
Stephani 2016	systematic literature review	high	Unclear (-1)	Unlikely	Unlikely	Unclear (-1)	Unclear	Moderate
Tang 2013	RCT	high	High (-2)	Unlikely	Unlikely	Unlikely	Unlikely	Moderate
Westergaard 2017	Qualitative study	moderate	Unclear (-1)	Unlikely	Unclear (-1)	Unlikely	Unlikely	Low
Yu 2014	cohort study	moderate	Unclear (-1)	High (-2)	Unlikely	Unlikely	Unlikely	Low
Zettl 2016	cohort study	moderate	Unclear (-1)	Unlikely	Unlikely	Unclear (-1)	Unlikely	Low

Search strategy for PubMed central

("phr"[All Fields] OR "personal health record"[All Fields] OR "patient portal"[All Fields]) AND (adult[All Fields] OR adult/10[All Fields] OR adult/100[All Fields] OR adult/11[All Fields] OR adult/111[All Fields] OR adult/15[All Fields] OR adult/18[All Fields] OR adult/18,19,49/see[All Fields] OR adult/18yrs[All Fields] OR adult/2[All Fields] OR adult/20[All Fields] OR adult/21[All Fields] OR adult/26[All Fields] OR adult/285[All Fields] OR adult/2cm2[All Fields] OR adult/3[All Fields] OR adult/32[All Fields] OR adult/36[All Fields] OR adult/3647446[All Fields] OR adult/3l[All Fields] OR adult/4,7,11/should[All Fields] OR adult/40[All Fields] OR adult/400[All Fields] OR adult/44[All Fields] OR adult/5[All Fields] OR adult/50[All Fields] OR adult/56[All Fields] OR adult/6[All Fields] OR adult/60[All Fields] OR adult/7[All Fields] OR adult/70[All Fields] OR adult/74[All Fields] OR adult/8[All Fields] OR adult/9[All Fields] OR adult/97[All Fields] OR adult/97egfp[All Fields] OR adult/a[All Fields] OR adult/acquired[All Fields] OR adult/activational[All Fields] OR adult/acute[All Fields] OR adult/ad[All Fields] OR adult/ad3[All Fields] OR adult/adenovirus[All Fields] OR adult/adolescent[All Fields] OR adult/adolescent/school[All Fields] OR adult/adolescents[All Fields] OR adult/adult[All Fields] OR adult/adult/senior[All Fields] OR adult/adult/senior/mixed[All Fields] OR adult/adult's[All Fields] OR adult/aged[All Fields] OR adult/ageing[All Fields] OR adult/aging[All Fields] OR adult/allogenic[All Fields] OR adult/always[All Fields] OR adult/and[All Fields] OR adult/animal[All Fields] OR adult/anoxia[All Fields] OR adult/apex[All Fields] OR adult/arrhythmic[All Fields] OR adult/assets[All Fields] OR adult/attending[All Fields] OR adult/authority[All Fields] OR adult/base[All Fields] OR adult/bcg/dtp/ipv/opv/mmr/dt/td[All Fields] OR adult/benign[All Fields] OR adult/bioline[All Fields] OR adult/bovine[All Fields] OR adult/bovine/chromaffin[All Fields] OR adult/breeding[All Fields] OR adult/bregma[All Fields] OR adult/c[All Fields] OR adult/cancer[All Fields] OR adult/canine[All Fields] OR adult/caregiver[All Fields] OR adult/carer[All Fields] OR adult/carer/parent[All Fields] OR adult/cat[All Fields] OR adult/cat/chromaffin[All Fields] OR adult/caterpillar[All Fields] OR adult/caucasian[All Fields] OR adult/caucasian/male[All Fields] OR adult/cd[All Fields] OR adult/cell[All Fields] OR adult/cercarial[All Fields] OR adult/chick[All Fields] OR adult/chick/egg[All Fields] OR adult/child[All Fields] OR adult/child/both[All Fields] OR adult/child/infant[All Fields] OR adult/child/neonate[All Fields] OR adult/child/senior[All Fields] OR adult/childhood[All Fields] OR adult/childhoodsepb[All Fields] OR adult/children[All Fields] OR adult/choose[All Fields] OR adult/chronic[All Fields] OR adult/classic[All Fields] OR adult/classical[All Fields] OR adult/clutch[All Fields] OR adult/cm[All Fields] OR adult/coach[All Fields] OR adult/college[All Fields] OR adult/commercial[All Fields] OR adult/community[All Fields] OR adult/contact[All Fields] OR adult/contemporary[All Fields] OR adult/control[All Fields] OR adult/cord[All Fields] OR adult/cordadult[All Fields] OR adult/cordretic[All Fields] OR adult/criminal[All Fields] OR adult/criminality[All Fields] OR adult/culture[All Fields] OR adult/cysticerci[All Fields] OR adult/dark[All Fields] OR adult/dauer[All Fields] OR adult/day[All Fields] OR adult/ddlt[All Fields] OR adult/de[All Fields] OR adult/deaf[All Fields] OR adult/deaf/hh[All Fields] OR adult/definitive[All Fields] OR adult/deformity[All Fields] OR adult/dementia[All Fields] OR adult/developed[All Fields] OR adult/developmental[All Fields] OR adult/diabetic[All Fields] OR adult/differentiated[All Fields] OR adult/disc[All Fields] OR adult/diseased[All Fields] OR adult/disposable[All Fields] OR adult/domicile[All Fields] OR adult/dual[All Fields] OR adult/dyspraxia[All Fields] OR adult/e17[All Fields] OR adult/early[All Fields] OR adult/educators[All Fields] OR adult/ee[All Fields] OR adult/egg[All Fields] OR adult/eggs/larvae/pupae[All Fields] OR adult/elder[All Fields] OR adult/elderly[All Fields] OR adult/elite[All Fields] OR adult/embryo[All Fields] OR adult/embryonic[All Fields] OR adult/emergence[All Fields] OR adult/emerging[All Fields] OR adult/erythroid[All Fields] OR adult/established[All Fields] OR adult/etiology[All Fields] OR

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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
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3-4
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.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
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.	4
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).	4
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.	13

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).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
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
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.	7-10
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
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.	7-10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13
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).	14
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).	14-15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
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.	15

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